Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults

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International Institute for Psychiatric Drug Withdrawal	General	General	General	The NICE committee should be congratulated for its work in this neglected area. However, there are several limitations to this guidance that should be addressed to make this guidance scientifically accurate and practically helpful. Historically, the long-term prescribing of drugs of dependence has not been central to primary care. The last 20 years have seen a tremendous change in GP psychotropic prescribing patterns. A recent analysis of all English NHS primary care prescription of antidepressants found a tripling of such GP activity, even after accounting for population growth, from 18.4 million items in 1998 to 70.9 million in 2018 (Bogowicz et al., 2021). Psychiatric treatment now occupies a great deal of primary care practice. Public Health England recently estimated 17% of the British adult population take antidepressants, with 26% of the adult population having been dispensed any prescribed drug of dependence in 2017-2018 (Public Health England, 2020). A 2017 Royal London survey of 250 UK GPs found they spent about 20% of their working time treating patients for stress, anxiety and depression; 85% of them reporting an increase over the past 5 years in	Thank you for your comment. The committee agrees that there are areas that may need support and investment, such as training costs, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines. During the scoping for this guideline, it was agreed that medicines such as antipsychotics are outside the remit of this guideline, due to the requirement for specialist management. Guidance on their safe prescribing is included within the NICE guideline for psychosis and schizophrenia in adults CG178, including some recommendations on stopping treatment (recommendations 1.4.6.3-1.4.6.5). This is reflected in the guideline scope and in responses to the scope consultation comments which are available on the NICE website. All references provided have been checked but are not relevant for inclusion in any of the guideline reviews. Either because they have been provided for information or do not meet the guideline review protocols, as they are not an appropriate study design for the relevant review.

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				the number of patients requiring such treatment. A 2018 Mind UK study that polled1,066 GPs found "GPs estimate that 4 in 10 (41 per cent) of their consultations now involve a mental health element". Therefore, GPs will need to care for many patients taking drugs of dependence. The Mind UK study, which focused on training needs, found GPs desired more training in mental health care, specifically "advice on starting and stopping patients' medication". Similarly, a 2013 study among Swedish GPs found they wanted more pharmacological and mental health prescribing information, specifically guidance on how to deprescribe drugs (Hedenrud et al., 2013). With their individual variances in dosing, treatment-emergent effects arising from dependence (Fava & Rafanelli, 2019), and withdrawal difficulties, drugs of dependence demand deeper pharmacological understanding and a new practice of close, frequent monitoring (Jha et al., 2018; Jha, 2019; Steinman et al., 2011; Steinman, 2013). GPs depend on updated NICE advice to prepare them for this unprecedented psychotropic era. We urge NICE to address the needs of GPs in advising optimal clinical practice regarding drugs of dependence.	

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				A last issue is that antipsychotics were not included in the scope of this review. The reason given by NICE was that this guidance would be more appropriate in the schizophrenia guideline (although this does not currently contain any advice on how to stop antipsychotics). However about half of antipsychotic prescriptions are given to people without a diagnosis of a psychotic condition, for conditions such as insomnia, anxiety, and others. It would be very helpful for these patients to have a guideline on how to stop antipsychotics because this is increasingly a concern for GPs and psychiatrists who wish to stop these medications when they are no longer useful (Cooper et al., 2019). It would be equally useful to have guidance on how to stop antipsychotics in people with a psychotic disorder for whom the benefits are outweighed by harms. Bogowicz, P., Curtis, H. J., Walker, A. J., Cowen, P., Geddes, J., & Goldacre, B. (2021). Trends and variation in antidepressant prescribing in English primary care: A retrospective longitudinal study. BJGP Open, 5(4), BJGPO.2021.0020. https://doi.org/10.3399/BJGPO.2021.0020	

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				Cooper, R. E., L. M. Grünwald, and M. Horowitz. 2020. "The Case for Including Antipsychotics in the UK NICE Guideline: 'Medicines Associated with Dependence or Withdrawal Symptoms: Safe Prescribing and Withdrawal Management for Adults.'" *Psychosis* 12 (1): 89–93. Fava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151 Gilchrist, J. (2017). Royal London Survey of Mental Health Services Provided by GPs. Royal London. Hedenrud, T. M., Svensson, S. A., & Wallerstedt, S. M. (2013). "Psychiatry is not a science like others"—A focus group study on psychotropic prescribing in primary care. BMC Family Practice, 14(1), 115. https://doi.org/10.1186/1471-2296-14-115 Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692	

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				Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047 Mind UK. (2018). GP mental health training survey Summary. Mind.org.uk. https://www.mind.org.uk/media-a/4414/gp-mh-2018-survey-summary.pdf Public Health England. (2020, December 3). Prescribed medicines review: Summary. GOV.UK. https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond	

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				the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x	
International Institute for Psychiatric Drug Withdrawal	Guideline	003-004	General	We are concerned that, as written, this guidance misinterprets 'dependence' with some unfortunate consequences that reverberate throughout the guidance and may adversely affect clinician-patient relationships and quality of care. The definition of dependence has become confounded as different professional bodies sought to define it according to their own perspectives, sometimes involving political considerations (Nielsen et al., 2012). However, the apolitical definitions in pharmacology texts such as *Goodman & Gilman's The pharmacological basis of therapeutics* are most useful. The body and brain adapt to the presence of a drug to maintain homeostasis. If a hormone or transmitter is increased, then the relevant receptor will be up or down-regulated so as to reduce the effect of the change to the equilibrium produced by the	Thank you for your comment. The context section has been reworded to clarify the definitions of dependence and addiction, as well as problems associated with dependence, which is used in the guideline recommendations. The guideline includes a recommendation on what should be discussed with the person before starting a medicine associated with dependence and withdrawal symptoms. This recommendation has been edited to include explaining that dependence is an expected phenomenon of these medicines but that some people may experience problems associated with dependence, what symptoms might be suggestive of problems associated with dependence. The recommendation already included discussing that with antidepressants and beneficial effects may occur slowly and they might experience side effects before noticing benefits, but many of these will ease over time. We believe the references you have provided are for information relevant to the points you made, however, these have also been checked for inclusion in our evidence

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				drug (Hyman and Nestler, 1996). This is a natural physiological process, not psychological or under the individual's volition, and should not be associated with addiction. This disambiguation of dependence was incorporated into the DSM-5 (O'Brien, 2011). It is important that both clinician and patient understand the natural process of adaptation leading to physiological dependence (sometimes called physical dependence), so as not to suggest the patient has developed an addiction and further, to communicate to the patient that some normal drug-related symptoms may arise and should be reported. When a psychotropic is taken regularly, certain clinically important phenomena related to the dependent state commonly emerge, such as loss of beneficial effect (tolerance) (Hyman and Nestler, 1996), inter-dose withdrawal, and withdrawal symptoms should dosing be irregular or reduced, as outlined in Monti, 2010 and Lerner and Klein, 2019 (latter authors associated with the US FDA). Patients should understand why they might have any of these symptoms and be urged by the clinician to report them promptly so they may be addressed appropriately (Steinman, 2013).	reviews. As they are descriptive articles/literature reviews rather than primary studies or systematic reviews of primary studies, they do not meet our prespecified protocol inclusion criteria.

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				Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. doi: 10.1007/s00340-005-2128-3. Lerner, A. and Klein, M. (2019) 'Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development', Brain Communications, (2019). doi: 10.1093/braincomms/fcz025. Monti, J. M., Floresco, S., Andrade, R., Cools, R., Roberts, A., Cador, M., Caillé, S., Stinus, L., & Jackson, A. (2010). Withdrawal Syndromes. In I. P. Stolerman (Ed.), Encyclopedia of Psychopharmacology (pp. 1370–1374). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-540-68706-1_162. Nielsen, M., Hansen, E. H. and Gotzsche, P. C. (2012) 'What is the difference between dependence and withdrawal reactions? A comparison of benzodiazepines and selective serotonin re-uptake inhibitors.', Addiction (Abingdon, England). England, 107(5), pp. 900–908. doi: 10.1111/j.1360-0443.2011.03686.x.	

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				O'Brien, C. (2011) 'Addiction and dependence in DSM-V', Addiction (Abingdon, England). 2010/10/06, 106(5), pp. 866–867. doi: 10.1111/j.1360-0443.2010.03144.x. Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	
International Institute for Psychiatric Drug Withdrawal	Guideline	010-011	016-021, 001-019	We are concerned that this recommendation (1.4) does not specify frequent regular medication reviews (1.4.1) or that the clinician closely monitor during the initiation phase or dosage changes of a drug of dependence (1.4.2). Rather than arranging review when the patient reports adverse effects as described in (1.4.3), the clinician should take the initiative to monitor closely and repeatedly (Jha et al., 2018; Jha, 2019; Steinman, 2013). NICE already deems regular medication reviews essential, but it has been shown prescribers are lax about recognizing the risks and monitoring for adverse effects and of psychotropics	Thank you for your comment. The committee's view is that the recommendations already include all of the points you raise. Recommendation 1.4.1 on the frequency of reviews does state that they need to be regular. This recommendation also includes a list of factors that indicate that more frequent

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				(Duncan et al., 2019; Sinclair et al., 2014; Treadwell et al., 2020), not being aware these drugs require a novel style of clinical attention. Historically, the long-term prescribing of drugs of dependence has not been not central to primary care. The last 20 years have seen a tremendous change in GP psychotropic prescribing patterns. A recent analysis of all English NHS primary care prescription of antidepressants found a tripling of such GP activity, from 18.4 million items in 1998 to 70.9 million in 2018, even after accounting for population growth (Bogowicz et al., 2021). Psychiatric treatment now occupies a great deal of primary care practice. Public Health England recently estimated 17% of the British adult population takes antidepressants, with 26% of the adult population having been dispensed any prescribed drug of dependence in 2017-2018 (Public Health England, 2020). A 2018 MindUK study that polled1,066 GPs found "GPs estimate that 4 in 10 (41 per cent) of their consultations now involve a mental health element". One way or the other, GPs will need to care for many patients taking drugs of dependence. With their individual variances in dosing, effects arising from dependence and non-adherence, and withdrawal difficulties, drugs of dependence	reviews will be required, including if the person is taking the medicine for the first time. Recommendation 1.4.2 states that the healthcare professional should consider increasing the frequency of reviews during dose adjustment. The committee agree it is important the review schedule is determined on the individual circumstances relevant to the person, and that required frequency would vary not only according to the medicine, but also for individuals. Therefore, they agreed it was not appropriate to recommend specific timeframes for frequency of review, but the need for regular review, with some situations requiring increased frequency is clearly stated in the recommendations. The guideline also includes recommendation on the content of reviews. These recommendations have been edited slightly to clarify that these should include consideration of both benefits and harms of the medicine, as well as other factors (such as signs the person is developing problems associated with dependence). The references you have provided have been checked for inclusion in our evidence reviews. We note many are provided for information relevant to the points raised and therefore are descriptive articles/literature reviews or conceptual analyses (Avery 2013, Bogowicz 2021, Cleare

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				demand deeper pharmacological understanding and a new practice of close monitoring during initiation or drug changes. This is essential to address serious adverse effects as soon as possible (Avery et al, 2015, Cleare et al., 2015 Jha et al., 2018; Jha, 2019; Steinman, 2013) (Figure 1). Some adverse drug effects upon initiation such as anxiety, jitteriness, activation, insomnia, hypomania, akathisia, serotonin toxicity, suicidality or, conversely, excessive somnolence or disorientation indicate the drug should be immediately reduced or discontinued (Carvalho et al., 2016; Hawkins, et al., 2021; Jha, et al., 2017; Luft, et al., 2018; Talton, 2020; Van Gestel, 2018; Zareifopoulos, et al., 2021. Clinicians should also be alert to physiological symptoms, such as gastrointestinal, genitourinary, sexual dysfunction, hyponatremia, skin rashes, bleeding, sweating, ophthalmic manifestations, and hyperprolactinemia, as well as such risks as liver damage (Carvalho et al., 2016). Clinician complacency leading to "set and forget" after antidepressant initiation is unwarranted, often with years going by without even annual review (Sinclair et al., 2014). Braund, et al.,	2008, the Jha and Steinman papers) or non-systematic reviews (Carvalho 2016, Hawkins 2021, Luft 2018, Zareifopoulos 2021) rather than primary studies or systematic reviews of primary studies and so do not meet the guideline protocol inclusion criteria. The comparators in Braund 2021 did not match protocol of the relevant review on Withdrawal symptoms (review C) as this study compared antidepressants to one another, rather than to no withdrawal or placebo as stated in the guideline review protocol. Sinclair 2014 did not meet the protocol criteria for the monitoring review as it is a non-comparative cohort study, therefore not relevant to either the intervention or qualitative element of the monitoring reviews included in the guideline. The topic covered by Talton 2020 and van Gastel 2020 was not relevant to any of the guideline review protocols. The study by Duncan 2019 does not address the objectives of the guideline monitoring review and therefore is not relevant to include there. Please note that the current recommendations were based on the evidence reviewed and committee experience, including knowledge of PHE report on prescribed medicine. The committee's view is that the recommendations made

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				2021 found that 8 weeks after initiating antidepressants, 11% of subjects suffered a burden of adverse effects such that they were moderately impaired to unable to function, and that this degree of burden interfered with treatment effectiveness. Initiation of a drug, dosage changes (including reduction), and drug changes are known to be the highest risk periods for adverse effects, requiring careful monitoring (Avery, 2013; GMC, 2021). It is the clinician's responsibility to advise the patient of this, as well as instruct the patient to report suspected adverse drug effects to the MHRA (GMC, 2021). This recommendation as written leaves the review process vague, giving clinicians no reason to remedy lax habits. NICE guidance should explicitly remind clinicians of best principles of clinical care. explicitly advising them to initiate frequent medication reviews (Steinman et al., 2011) and encourage collaborative care (Cleare et al., 2015; Steinman, 2013), asking patients to report to them (and MHRA) any significant drug adverse effects, particularly those that diminish daily functioning, worsen with additional doses, or are otherwise incapacitating (GMC, 2021; Steinman, 2013).	within the guideline are consistent with the relevant recommendations made in the PHE report.

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				Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368 Bogowicz, P., Curtis, H. J., Walker, A. J., Cowen, P., Geddes, J., & Goldacre, B. (2021). Trends and variation in antidepressant prescribing in English primary care: A retrospective longitudinal study. BJGP Open, 5(4), BJGPO.2021.0020. https://doi.org/10.3399/BJGPO.2021.0020 Braund, T. A., Tillman, G., Palmer, D. M., Gordon, E., Rush, A. J., & Harris, A. W. F. (2021). Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: An iSPOT-D report. Translational Psychiatry, 11(1), 417. https://doi.org/10.1038/s41398-021-01533-1 Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychotherapy	

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				and Psychosomatics, 85(5), 270–288. https://doi.org/10.1159/000447034 Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093 Duncan, P., Cabral, C., McCahon, D., Guthrie, B., & Ridd, M. J. (2019). Efficiency versus thoroughness in medication review: A qualitative interview study in UK primary care. British Journal of General Practice, 69(680), e190–e198. https://doi.org/10.3399/bjgp19X701321 GMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-	

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				/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf Hawkins, E. M., Coryell, W., Leung, S., Parikh, S. V., Weston, C., Nestadt, P., Nurnberger, J. I., Kaplin, A., Kumar, A., Farooqui, A. A., El-Mallakh, R. S., & For the National Network of Depression Centers Suicide Prevention Task Group. (2021). Effects of somatic treatments on suicidal ideation and completed suicides. Brain and Behavior. https://doi.org/10.1002/brb3.2381 Jha, M. K., Minhajuddin, A., South, C., Rush, A. J., & Trivedi, M. H. (2017). Worsening Anxiety, Irritability, Insomnia, or Panic Predicts Poorer Antidepressant Treatment Outcomes: Clinical Utility and Validation of the Concise Associated Symptom Tracking (CAST) Scale. International Journal of Neuropsychopharmacology, 21(4), 325–332. https://doi.org/10.1093/ijnp/pyx097 Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692	

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				Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047 Luft, M. J., Lamy, M., DelBello, M. P., McNamara, R. K., & Strawn, J. R. (2018). Antidepressant-Induced Activation in Children and Adolescents: Risk, Recognition and Management. Current Problems in Pediatric and Adolescent Health Care, 48(2), 50–62. https://doi.org/10.1016/j.cppeds.2017.12.001 Mind UK. (2018). GP mental health training survey Summary. Mind.org.uk. https://www.mind.org.uk/media-a/4414/gp-mh-2018-survey-summary.pdf Public Health England. (2020, December 3). Prescribed medicines review: Summary. GOV.UK. https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary Sinclair, J. E., Aucott, L. S., Lawton, K., Reid, I. C., & Cameron, I. M. (2014). The monitoring of	

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				longer term prescriptions of antidepressants: Observational study in a primary care setting. Family Practice, 31(4), 419–426. https://doi.org/10.1093/fampra/cmu019 Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Talton, C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042 Treadwell, J. S., Wong, G., Milburn-Curtis, C., Feakins, B., & Greenhalgh, T. (2020). GPs'	

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				understanding of the benefits and harms of treatments for long-term conditions: An online survey. BJGP Open, bjgpopen20X101016. https://doi.org/10.3399/bjgpopen20X101016 Van Gastel, A. (2018). Drug-Induced Insomnia and Excessive Sleepiness. Sleep Medicine Clinics, 13(2), 147–159. https://doi.org/10.1016/j.jsmc.2018.02.001 Zareifopoulos, N., Katsaraki, M., Stratos, P., Villiotou, V., Skaltsa, M., Dimitriou, A., Karveli, M., Efthimiou, P., Lagadinou, M., & Velissaris, D. (2021). Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic. European Review for Medical and Pharmacological Sciences, 25(14), 4746–4756. https://doi.org/10.26355/eurrev_202101_26386	
International Institute for Psych	Guideline	007-008	019-029, 001-004	We are concerned that this recommendation (1.3.3) does not advise clinicians to warn patients against taking drugs of dependence inconsistently. Within weeks, patients taking these drugs regularly will become neurobiologically adapted	Thank you for your comment. The committee agree this is important to highlight and a statement has been added to recommendation 1.3.1 to include this information in the discussion with the person before starting treatment. This is also covered within the NICE guidelines for Medicines

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iatric Drug Withdrawal				to them and physiologically dependent, as explained in the guidance's Context. Accidentally forgetting doses, skipping them, or taking them off-schedule may incur unpleasant withdrawal symptoms (NICE, 2021), which may be mistaken by the patient or clinician as intensifying symptoms of the original complaint, loss of effect, or onset of a new medical condition, occasioning the expense and risk of inappropriate medical care and prescription escalation (Demyttenaere & Haddad, 2000; Ho et al., 2016; Meijer et al., 2001). Non-adherence can also lead to treatment resistance or iatrogenic pseudo-resistance (Fava et al., 2020; Howes et al., 2021). The neurobiological basis for the adverse effects of irregular dosing of psychotropics is explained in Horowitz & Taylor, 2022 and Sørensen et al., 2021 in their discussions of changes in receptor occupancy and drug plasma saturation in relation to dosing changes. Departures from a regular dosing schedule would not be a rare occurrence among patients. Estimates for patient non-adherence to antidepressants run as high as 50% (Ho et al., 2016). This type of patient behavior is also common with other psychiatric drugs, with adverse drug effects being a common patient	adherence and Medicines optimisation which are cross-referred to in the section for reviewing medicines. The references you have provided have also been checked for inclusion in our evidence reviews. We note that most are provided for information relevant to the points you raise, and therefore do not meet the guideline protocol criteria due to being descriptive articles/literature reviews rather than primary studies or systematic reviews of primary studies (Cleare 2008, Demyttenaere 2000, Fava 2020, Howes 2021). Meijer 2001 was not relevant to include in the withdrawal symptoms review as it was a non-comparative cohort study. Ho 2016, Semahegn 2020 and Sørensen 2021 are systematic reviews the aim and PICO of which did not match any of the guideline review questions. Horowitz and Taylor 2022 will not be published till February 2022; however, it appears to be a descriptive article that would therefore not meet the study inclusion criteria for the relevant review questions.

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				motivation for missing doses; lack of clinician follow-up is a key factor in patient non-adherence (Semahegn et al., 2020). As written, this recommendation is incomplete. Clinicians should caution patients to take their drugs on a consistent daily schedule, that taking the drugs inconsistently may result in unpleasant symptoms due to physiological dependence and withdrawal, and emphasise any irregularity in dosing should be reported by the patient. Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093 Demyttenaere, K., & Haddad, P. (2000). Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 101(s403), 50–56.	

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				Meijer, W. E. E., Bouvy, M. L., Heerdink, E. R., Urquhart, J., & Leufkens, H. G. M. (2001). Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. British Journal of Psychiatry, 179(6), 519–522. https://doi.org/10.1192/bjp.179.6.519 NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90 Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020). Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: A systematic review and meta-analysis. Systematic Reviews, 9. https://doi.org/10.1186/s13643-020-1274-3 Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review.	

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				Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-w Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	
International Institute for Psychiatric Drug Withdrawal	Guideline	015-016	029-030 001-007	As written, this guidance (1.5.13) provides sensible basic information that should be enhanced further. It should include this proviso: "- Antidepressant withdrawal symptoms can be delayed in onset, especially for drugs with a long half-life like fluoxetine, or they may not immediately be recognized by the patient (Chouinard & Chouinard, 2015) (being mistaken for common ailments such as flu, food poisoning, eyestrain, etc.). " The Guidance should include examples of the new symptoms, e.g. dizziness, headache, 'electric zaps', otherwise GPs will not know what to look for. Sources such as Chouinard & Chouinard, 2015; Haddad & Anderson, 2007,	Thank you for your comment. The recommendation about discussing withdrawal symptoms with the person has been amended to include that withdrawal symptoms can vary widely in type, severity and timing. It also now includes stating that some may persist over a prolonged period. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms, if new, did not require any further investigation.

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				Lerner and Klein, 2019 provide lists of possible symptoms that may be condensed for easy reference. Psychological or emotional withdrawal symptoms, such as anxiety, depressed mood, and insomnia, are easily mistaken for a return of the underlying condition, rather than attributed to physiological withdrawal symptoms (Hyman and Nestler, 1996; Lerner and Klein, 2019). But the temporal relationship to dosage change, a novel presentation, or co-occurring physical withdrawal symptoms would indicate the source is withdrawal. It is important for guidelines to explain this or patients are highly likely to be misdiagnosed as having relapsed and restarted on unnecessary medication (Haddad & Anderson, 2007). An important point of information for clinicians is that withdrawal symptoms are normally improved very quickly by re-starting the medication, whereas depression takes weeks or longer – this can allow identification of withdrawal symptoms, at least retrospectively. Guidance should help update clinician's knowledge regarding misdiagnosis of relapse. It long has been thought if symptoms are long-lasting, they must be relapse but, as now recognised by the draft NICE CG90 on	This has now been detailed in the rationale for that section. The references provided related to this point (Chouinard, Haddad & Anderson and Lerner & Klein) do not meet the protocol requirements for this evidence review due to not being the appropriate study designs. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary. All references provided have been checked but did not meet the guideline review protocol for the withdrawal symptoms review due to their respective study designs. The committee are aware of the draft NICE guideline for depression. At the time of responding to these comments, this update was still in development.

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				depression, withdrawal syndrome can be severe and protracted (NICE, 2021). Symptom longevity should no longer be considered a sign of relapse. As many patients report being told that because their withdrawal symptoms are severe or long-lasting, they have relapsed, this very common misdiagnosis has a number of unfortunate consequences (Framer, 2021; Guy et al., 2020). Chouinard, G., & Chouinard, V.-A. (2015). New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. Psychotherapy and Psychosomatics, 84(2), 63–71. https://doi.org/10.1159/000371865 Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274 Guy, A. et al. (2020) 'The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition', Therapeutic Advances in Psychopharmacology. SAGE Publications Ltd	

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				STM, 10, p. 204512532096718. doi: 10.1177/2045125320967183. Haddad, P. M., & Anderson, I. M. (2007). Recognising and managing antidepressant discontinuation symptoms. Advances in Psychiatric Treatment, 13(6), 447–457. https://doi.org/10.1192/apt.bp.105.001966 Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. doi: 10.1007/s00340-005-2128-3. Lerner, A., & Klein, M. (2019). Dependence, withdrawal and rebound of CNS drugs: An update and regulatory considerations for new drugs development. Brain Communications, 1(1). https://doi.org/10.1093/braincomms/fcz025 NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90	

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International Institute for Psychiatric Drug Withdrawal	Guideline	005	007-014	We are concerned that, as written, this recommendation (1.2.2) may incorrectly imply that the development of physiological dependence on a drug is related to a mental health diagnosis or addictive tendency. Although line 13 correctly discourages prescription on the basis of vague or incorrect diagnosis, any diagnosis, including "comorbid mental health diagnosis" (line 11), is not relevant to development of physiological dependency. Anyone may develop physiological dependency on any opioid, benzodiazepine, gabapentinoid, Z-drug or antidepressant, with any variety of co-existing conditions, no prior history of drug misuse or dependency required. This is because it is a physiological response to a change in neurotransmitter levels and is not dependent on the psychology of the individual. For example, people become physiologically dependent on caffeine no matter their personality, past history of drug abuse, social circumstances, etc – the same principles apply to the drugs in this review. In the Context section's (accurate) definition -- dependence is a physiological state characterized by tolerance and withdrawal -- there is no place for a psychological component. A mental health diagnosis is not implicated in	Thank you for your comment. This recommendation was based on evidence from prognostic reviews, in evidence review E. Prognostic evidence from studies of opioids and benzodiazepines demonstrated an increased risk of developing problems associated with dependence in people diagnosed with mental health disorders including depression, anxiety, post-traumatic stress disorder, bipolar disorder, alcohol-use disorder or drug-misuse disorder. The committee agreed, based on their experience, that this also applies to Z drugs and gabapentinoids, but not to antidepressants, which are not dependence-forming medicines. The committee also noted that a comorbid mental health diagnosis can have a profound impact on people and increase their desire for medicines, and that people with a history of drug misuse may need higher drug doses to obtain the desired effect. This is stated in the rationale for the recommendation and in the discussion of the evidence in review E. It is important to note that this recommendation states the increased risk is for *problems associated with dependence*, not the development of dependence itself. This is consistent with the definitions in the context. The rationale also stated that while these factors should be considered, these factors alone should not be a barrier to

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				the cellular process of tolerance or the physiological process of withdrawal (O'Brien, 2011; O'Brien, 2018). Psychologically driven compulsion leading to drug-seeking is the extra aspect needed to meet the definition of addiction (O'Brien, 2018). People can become physiologically dependent – a natural biological process – without having this psychological drive. The crux is that dependence may occur in anyone who repeatedly uses a drug that causes adaptation. It is not dependent on their diagnosis, personality, habits or inclinations – it depends simply on the sensitivity of their neural tissue to drug effects. Also important for clinicians to understand is that taking any of these drug classes precisely as their doctor recommends may still develop physiological dependence and therefore be at risk of withdrawal (as will be clear to anyone who takes caffeine each morning and tries to stop it). The implication throughout this document that there are sociologically defined groups at higher risk of physiological dependence erroneously conflates physiological dependence with the psychological drivers associated with addiction. This shifts the clinician's attention from the effect	prescribing. This has now been added to the recommendation. The references you have provided have also been checked for inclusion in our evidence reviews. We note that the O'Brien papers are provided for information regarding the definition of dependence rather than as relevant papers to include. Please note that in evidence review A (Patient Information) that part of the Buchman 2016 population is applicable, data saturation was reached meaning that as a large number of papers were identified for this review, inclusion of papers was halted once no new information emerged from studies that were found to match the review protocol. The themes emerging from the study including the need for empathy and non-judgmental support from health care professionals have been captured by the evidence included in evidence review A, and were acknowledged by the committee and reflected in the recommendations.

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				of long-term drug use on neural (and other) tissue and safe deprescribing to inappropriate addiction treatment. Buchman, et al., 2016 describe the corrosive effect of this stigmatization on the clinician-patient relationship. Therefore, the framing of this guidance towards suspicion of people who may have a "comorbid" tendency toward drug abuse will lead GPs to miss the central issue: The majority of people at risk of withdrawal are taking medications as prescribed. We urge the committee to make the sense of this recommendation consistent with their own definition of dependence in the Context section. As written, the sense of this section is unclear and may misinform clinicians to the detriment of quality of care. Buchman, D. Z., Ho, A., & Illes, J. (2016). You Present like a Drug Addict: Patient and Clinician Perspectives on Trust and Trustworthiness in Chronic Pain Management. Pain Medicine: The Official Journal of the American Academy of Pain Medicine, 17(8), 1394–1406. https://doi.org/10.1093/pm/pnv083 O'Brien, C. (2011) 'Addiction and dependence in DSM-V', Addiction (Abingdon, England).	

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				2010/10/06, 106(5), pp. 866–867. doi: 10.1111/j.1360-0443.2010.03144.x. O'Brien, C. P. (2018). Chapter 24: Drug Use Disorders and Addiction. In L. L. Brunton, R. Hilal-Dandan, & B. C. Knollmann (Eds.), Goodman & Gilman's The pharmacological basis of therapeutics. (13th ed.). McGraw-Hill Medical.	
International Institute for Psychiatric Drug Withdrawal	Guideline	005	003-006	We commend NICE for reminding clinicians that watchful waiting and non-pharmacological treatments are among management options for patients taking drugs of dependence. *Before starting or continuing treatment with an opioid, benzodiazepine, gabapentinoid, Z-drug or antidepressant , ensure that all relevant management options, including non-pharmacological treatment and watchful waiting, have been discussed with and offered to the person.* The issue in this section is the word "continuing". "Non-pharmacological treatment or watchful waiting" might not be best care when treatment-emergent symptoms arise, as dosage reduction or discontinuation of a psychotropic may be the appropriate intervention.	Thank you for your comment. The committee agreed that this recommendation should apply throughout the management pathway. For example, if a healthcare professional takes on the prescribing responsibility for a person who is already receiving these medicines, they should ensure all suitable treatment options have been discussed. The inclusion of the word 'suitable' (previously worded as 'relevant') should be interpreted with the healthcare professional's clinical judgement and knowledge of condition-specific guidelines,

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				We are concerned that, as written, this recommendation (1.2.1) may reassure clinicians in postponing action on treatment-emergent symptoms that may be due to drug adverse effects in favor of "watchful waiting" or referral of the patient to "non-pharmacological treatment". Further, this section does not advise the clinician to so inform the patient about potential treatment-emergent drug adverse effects and measures that might be taken to address them. Even in the early stages of treatment, clinicians should not be complacent that any adverse drug effects are likely to ease over time, responding with "watchful waiting". The common prescriber tendency to "set and forget" after antidepressant initiation, often refilling prescriptions for years without even annual review (Sinclair et al., 2014), is unwarranted, as it is with all prescribed psychotropics. Adverse effects may often improve over time because of neurobiological adaptation to the presence of the drug (Cleare et al., 2015), which is evidence of tolerance and dependence. However, they do not always resolve and are not always tolerable. Braund, et al., 2021 found that 8 weeks after initiating antidepressants, 11% of subjects suffered a burden of adverse effects such that they were moderately impaired to unable to function, and	including the NICE guideline on depression which is being updated (at the time of responding to these comments). Section 1.5 on withdrawal medicines includes recommendations about identification and management of withdrawal symptoms and should be followed in this situation. Furthermore, the section on information support 1.3 highlights that the potential to develop side effects should be discussed, and what to expect if they do occur. The section on reviewing medicines (1.4) highlights that potential for adverse effects should be one of the considerations for more frequent review, and is a prompt for an unscheduled review. Recommendations include stating that decisions made about continuing, adjusting the dose or stopping medicine should be made based on benefits and harms the person is experiencing (amongst other factors). Therefore, the committee's view is that the guideline recommendations reiterate the need for consideration of adverse effects of the medicine and does not imply that they would be overlooked in favour of watchful waiting or referral to non-pharmacological treatment. The committee agree that medicines adherence is an important aspect to promote, and a statement has been added to recommendation 1.3.1 to include this information in the discussion with the person before starting treatment. This is also covered within the NICE guidelines for Medicines

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				that this degree of burden interfered with treatment effectiveness. Some adverse drug effects such as anxiety, jitteriness, activation, insomnia, hypomania, akathisia, serotonin toxicity, suicidality or, conversely, excessive somnolence or disorientation indicate the antidepressant should be immediately reduced or discontinued (Carvalho et al., 2016; Fava & Rafanelli, 2019; Hawkins, et al., 2021; Jha, et al., 2017; Luft, et al., 2018; Talton, 2020; Van Gestel, 2018; Zareifopoulos, et al., 2021. Clinicians should also be alert to physiological symptoms, such as gastrointestinal, genitourinary, sexual dysfunction, hyponatremia, skin rashes, bleeding, sweating, ophthalmic manifestations, and hyperprolactinemia, indicating serious systemic adverse effects, as well as such risks as liver damage (Carvalho et al., 2016). After the initiation phase, one extremely common drug adverse effect in particular may call for patient education. Within weeks, patients taking these drugs regularly will become neurobiologically adapted to them and physiologically dependent, as explained in the guidance's Context. Once a regular drug schedule is established and the person is adapted to the drug, irregular dosing – skipped	adherence and Medicines optimisation which are cross-referred to in the section for reviewing medicines. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note that most are provided as information to support points raised and are therefore not relevant to include within the review questions being descriptive articles/literature reviews or conceptual analyses rather than primary studies or systematic reviews of primary studies or non-systematic reviews (Avery 2013, Bogowicz 2021, Cleare 2008, Demyttenaere 2000, Fava 2020, Howes 2021,Jha 2018 Steinman 2011, Carvalho 2016,Hawkins 2021, Luft 2018, Khalil 2020, Zareifopoulos 2021). The comparators in Braund 2021 did not match protocol of the relevant review on Withdrawal symptoms (review C) as this study compared antidepressants to one another, rather than to no withdrawal or placebo as stated in the guideline review protocol. The study design of studies included in the systematic review by Panagioti 2019 did not match relevant review protocols in this guideline. Meijer 2001 and Sinclair 2014 did not meet the protocol criteria for the monitoring review as it is a non-comparative cohort study, therefore not relevant to either the intervention

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				or delayed doses, taking an incorrect dose – may evoke withdrawal symptoms (NICE, 2021) reported to the clinician as mysterious psychological or physiological symptoms. The neurobiological basis for the adverse effects of irregular dosing of psychotropics is explained in Horowitz & Taylor, 2022 and Sørensen et al., 2021 in their discussions of changes in receptor occupancy and drug plasma saturation in relation to dosing changes. Estimates for patient non-adherence to antidepressants run as high as 50% (Ho et al., 2016). This type of patient behavior is also common with other psychiatric drugs; lack of clinician follow-up is a key factor (Semahegn et al., 2020). In the absence of clinician recognition and appropriate action, non-adherence may be expected to continue, potentially bringing about the additional risk and expense of inappropriate medical care and prescription escalation. Treatment resistance or iatrogenic pseudo-resistance (Fava et al., 2020; Howes et al., 2021) is another potential outcome of inconsistent dosing. A clinician who ascertains non-adherence should carefully explain the circumstance of physiological dependence, and specifically advise patients to take their drugs on a	or qualitative element of the monitoring reviews included in the guideline. The objectives of Talton and van Gastel 2020 were not relevant to any of the guideline review protocols. Ho 2016, Semahegn 2020 and Sørensen 2021 were systematic reviews the aim and PICO of which did not match any of the guideline review questions. Horowitz and Taylor 2022 will not be published till February 2022; however, it appears to be a descriptive article that would therefore not meet the study inclusion criteria for the relevant review questions.

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				consistent schedule (Demyttenaere & Haddad, 2000; Ho et al., 2016; Meijer et al., 2001). As written, this recommendation is incomplete. It is the clinician's responsibility to advise the patient of the potential for treatment-emergent adverse effects and actively monitor the maintenance phase as well as the high-risk periods during drug dosage increase, decrease, or change (Steinman, et al., 2011; Steinman; 2013). The patient should be advised to also report suspected adverse drug effects to the MHRA (GMC, 2021). Along with recognizing the value of watchful waiting and non-pharmacological interventions, clinicians should also be aware that vague symptoms may be adverse effects of the drug or arise from physiological dependence that require other clinical strategies, including cessation of the drug (in a gradual manner). Therefore it may be prudent in this section to include an additional point referring to the possibility of ceasing the drug of dependence if adverse symptoms arise, and that these should be monitored – at the beginning of treatment and throughout the course of treatment, rather than an inherent assumption that these drugs should be 'continued.'	

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				Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368 Braund, T. A., Tillman, G., Palmer, D. M., Gordon, E., Rush, A. J., & Harris, A. W. F. (2021). Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: An iSPOT-D report. Translational Psychiatry, 11(1), 417. https://doi.org/10.1038/s41398-021-01533-1 Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychotherapy and Psychosomatics, 85(5), 270–288. https://doi.org/10.1159/000447034 Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting.	

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				and Adolescents: Risk, Recognition and Management. Current Problems in Pediatric and Adolescent Health Care, 48(2), 50–62. https://doi.org/10.1016/j.cppeds.2017.12.001 Meijer, W. E. E., Bouvy, M. L., Heerdink, E. R., Urquhart, J., & Leufkens, H. G. M. (2001). Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. British Journal of Psychiatry, 179(6), 519–522. https://doi.org/10.1192/bjp.179.6.519 NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90 Panagioti, M., Khan, K., Keers, R. N., Abuzour, A., Phipps, D., Kontopantelis, E., Bower, P., Campbell, S., Haneef, R., Avery, A. J., & Ashcroft, D. M. (2019). Prevalence, severity, and nature of preventable patient harm across medical care settings: Systematic review and meta-analysis. BMJ, l4185. https://doi.org/10.1136/bmj.l4185	

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				Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020). Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: A systematic review and meta-analysis. Systematic Reviews, 9. https://doi.org/10.1186/s13643-020-1274-3 Sinclair, J. E., Aucott, L. S., Lawton, K., Reid, I. C., & Cameron, I. M. (2014). The monitoring of longer term prescriptions of antidepressants: Observational study in a primary care setting. Family Practice, 31(4), 419–426. https://doi.org/10.1093/fampra/cmu019 Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-w Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. *Journal of the American Geriatrics Society*, *59*(8), 1513–	

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				1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965 Talton, C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042 Van Gastel, A. (2018). Drug-Induced Insomnia and Excessive Sleepiness. Sleep Medicine Clinics, 13(2), 147–159. https://doi.org/10.1016/j.jsmc.2018.02.001 Zareifopoulos, N., Katsaraki, M., Stratos, P., Villiotou, V., Skaltsa, M., Dimitriou, A., Karveli, M., Efthimiou, P., Lagadinou, M., & Velissaris, D. (2021). Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic. European Review for Medical and	

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				Pharmacological Sciences, 25(14), 4746–4756. https://doi.org/10.26355/eurrev_202101_26386	
International Institute for Psychiatric Drug Withdrawal	Guideline	005	015	We are concerned that this recommendation (1.2.3) implies that a low dose of a psychotropic alone is protective against development of physiological dependence. This is not so. It is not clear what factors increase a person's risk of physiological dependence. Length of time on the drug is certainly a key factor. All people will become physiologically dependent on these substances if they are used for long enough (Hyman and Nestler, 1996; O'Brien, 2011). Later on, this is made explicit in the guidance when it correctly recommends all patients be told 'dependence is an expected effect of these medications'. That statement is true and applies to anyone at any dosage level. Good medical practice decrees drugs be prescribed at the lowest effective dosage for the shortest amount of time (Schiff, 2011; Stampfer, et al., 2019), with close monitoring and frequent medication review to identify drug adverse effects, including lack of benefit resulting from drug tolerance and apparent relapse from inconsistent dosing (Steinman, 2013).	Thank you for your comment. The recommendation you refer to has been moved to sit within the prescribing strategies recommendations (1.3) and the reference to starting at a low dose no longer sits within the recommendation about taking steps to minimise problems associated with dependence. The committee agree that dependence is an expected phenomena of these medicines, this recommendation therefore focusses on the risk of developing problems associated with dependence, for which evidence was available. This statement retained in recommendation 1.3.8 which recommends starting with a low dose and agree frequent, regular reviews, which is consistent with your comment. The references you have provided have been checked for inclusion in the guideline evidence reviews although we note many are provided for information in reference to specific points made and therefore due to being descriptive articles/guidance they do not meet any of the protocol study

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				Sinclair et al., 2014 found the number of patients not receiving medication review steadily increases from 20% in the second year of antidepressant prescription to about 90% in the tenth year, showing increasing numbers of patients do not get even an annual review. Duncan, et al., 2019 found medication reviews were often cursory. Both of these studies were conducted in UK primary care practices. As prescribers often do not follow good clinical practice concerning psychotropics, reminders should be explicit in the guidance, particularly of close monitoring to identify and remedy problems associated with dependence (Jha et al., 2018; Jha, 2019; Steinman, 2013). Clinicians should not be complacent about dependence-inducing drugs at any dosage. Duncan, P., Cabral, C., McCahon, D., Guthrie, B., & Ridd, M. J. (2019). Efficiency versus thoroughness in medication review: A qualitative interview study in UK primary care. British Journal of General Practice, 69(680), e190–e198. https://doi.org/10.3399/bjgp19X701321 Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. Doi: 10.1007/s00340-005-2128-3.	design inclusion criteria (Hyman 1996, Schiff 2011, Jha and Steinman papers, Obbrien 2011 and Stampfer 2019). The study by Duncan 2019 does not address the objectives of the guideline monitoring review and therefore is not relevant to include there. Sinclair 2014 was also not relevant to include in this review as it is a non-comparative cohort study, therefore not relevant to include in either the intervention or qualitative element of the monitoring reviews included in the guideline.

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				Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047 O'Brien, C. (2011) 'Addiction and dependence in DSM-V', Addiction (Abingdon, England). 2010/10/06, 106(5), pp. 866–867. Doi: 10.1111/j.1360-0443.2010.03144.x. Schiff, G. D. (2011). Principles of Conservative Prescribing. Archives of Internal Medicine, 171(16), 1433. https://doi.org/10.1001/archinternmed.2011.256 Sinclair, J. E., Aucott, L. S., Lawton, K., Reid, I. C., & Cameron, I. M. (2014). The monitoring of longer term prescriptions of antidepressants: Observational study in a primary care setting.	

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				Family Practice, 31(4), 419–426. https://doi.org/10.1093/fampra/cmu019 Stampfer, H. G., Gabb, G. M., & Dimmitt, S. B. (2019). Why maximum tolerated dose? British Journal of Clinical Pharmacology, 85(10), 2213–2217. https://doi.org/10.1111/bcp.14032 Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	
International Institute for Psychiatric Drug Withdrawal	Guideline	006	006-015	We are concerned that this advice (1.2.7) as written does not address the situation where the patient might have been taking a drug of dependence for some time and wish to discontinue even if, in the clinician's opinion, discontinuation is not in the patient's best interest. "People have a right to refuse any treatment", according to NICE NG197 Shared decision making. When a drug of dependence is involved, even if the clinician does not agree	Thank you for your comment. The committee agree this is an important situation to consider. These guidelines are intended to improve safe prescribing of medicines associated with dependence and withdrawal symptoms and improve care for people who are prescribed these medicines. An individual's preference to withdraw from the medicine they are taking is promoted by the guideline. The recommendation you highlight is about the variables that a clinician should consider before starting the prescription of a medicine. However, shared decision making, and consideration of the

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				with the patient's decision, the clinician should assist the patient in tapering off the drug so as not to cause worsening of the patient's condition in the form of withdrawal symptoms. As written, this recommendation is incomplete. We urge addition of a provision addressing a patient's wish to discontinue a drug of dependence with gradual tapering to 46andomiz risk of withdrawal syndrome, even if in the clinician's opinion this is not in the person's best interest. NICE. (2021). NG197 Shared decision making. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. www.nice.org.uk/guidance/ng197	person's preference is a key factor. In the section on content of reviews recommendation 1.4.5 states that the decision to continue, adjust the dose or stop should be based on benefits and harms, and signs they are developing problems with dependence and the persons preference. Recommendation 1.5.1 also includes the person wanting to stop as a reason to discuss withdrawal.
International Institute for Psychiatric Drug Withdrawal	Guideline	007	002-012	We are concerned that this recommendation (1.3.1) incorrectly excludes antidepressants from drugs that may incur physiological dependence, occluding clinician understanding of risk and clarity of communication to the patient: *if the medicine is an opioid, benzodiazepine, gabapentinoid or Z-drug:* − *the risk of developing dependence* − *the symptoms and signs of dependence* − *the risk of developing tolerance*	Thank you for your comment. The committee disagree that antidepressants are incorrectly excluded from dependence forming medicines. As stated in the context for this guideline, and in the scope, antidepressants are historically not classified as dependence-forming medicines, although they can nevertheless cause withdrawal symptoms when they are stopped. This is consistent with other reports on this topic, for example the Public Health England Prescribed Medicines Review published in 2019.

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				There is neuroimaging evidence of adaptation to antidepressants in the form of down-regulation of serotonergic receptors – in effect, in vivo, evidence of tolerance (and dependence) (Meyer, et al., 2001, Haahr et al., 2014), consistent with pharmacological definitions of dependence. The exact nature of neurobiological adaptation to antidepressants has received relatively little study, but it is thought to involve down-regulation of serotonergic receptors in response to higher levels of synaptic serotonin arising as a consequence of serotonin transporter (SERT) antagonism, the primary target of antidepressants.(Olver, Burrows and Norman, 1999; Renoir, 2013) There is evidence this occurs in humans: even short-term SSRI use causes reduces the sensitivity of cortical 5-HT2A receptors (Meyer et al., 2001) in depressed patients and 5-HT4 receptor in healthy controls (Haahr et al., 2014) as measured by PET binding studies. Although this phenomenon has not been studied in humans, in animals, long-term treatment with antidepressants produces a reduction in endogenously 47andomized47 levels of serotonin detected (Bosker et al., 2010) after an initial increase (Kitaichi et al., 2010). There are many other systems downstream of effects at the target receptor, including	The references you have provided have been checked for inclusion in the guideline evidence reviews. We note that most are provided for information in support of points made and therefore are descriptive articles/literature reviews or conceptual analyses rather than primary studies or systematic reviews of primary studies and so not relevant to include in any guideline evidence reviews(e.g., Fava 2020, Howes 2021, Olver 1999). Meyer et al. 2001, Haahr et al. 2014 and Solomon et al., 2005 is not relevant to the objectives of any of the guideline review questions. Brath 2018, Ho 2016, Kinrys 2019, Renoir 2013 are systematic reviews the aim and PICO of which did not match the guideline review protocols. Studies included in the systematic reviews also did not match the study design prespecified in the guideline review protocols. .

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				norepinephrine, dopamine, glutamate and GABA-ergic pathways, which may also adapt to long-term administration of antidepressants.(Renoir, 2013) Antidepressants are clearly associated with tolerance. In one longitudinal study it was observed that 25% of patients required increased dosages of antidepressant over time,(Solomon et al., 2005) consistent with the development of tolerance. A systematic review found that rates of tachyphylaxis (used as a synonym for tolerance by some sources) occurred in 9% to 57% of patients with depression treated with antidepressants.(Kinrys et al., 2019) Physiological dependence is implicated in the adverse effects of non-adherence, an extremely frequent behavior estimated to occur in 50% of patients (Ho et al., 2016). Patients should be informed about the natural development of physiological dependence and risk of withdrawal effects while being cautioned against accidental or deliberately inconsistent dosing, forgetting or skipping doses, or taking them off-schedule, as they may experience withdrawal symptoms (NICE, 2021) that can be misinterpreted by clinician and patient alike as lack of psychiatric drug treatment effect (Fava et al., 2020; Howes	

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				et al., 2021) or a worsening psychiatric condition (Fava & Rafanelli, 2019), resulting in inappropriate treatment, such as a prescription cascade (Brath et al., 2018). It is therefore inaccurate to exclude antidepressants from the class of the other dependence-forming drugs. As with the other drug classes, patients who are starting antidepressants should be warned about dependence and to report withdrawal symptoms, the cardinal sign of physiological dependence, should the drug be taken inconsistently or dosage reduced (O'Brien, 2018). It is not pharmacologically accurate to exclude them from this category of medications. Bauer, R., Glenn, T., Alda, M., Sagduyu, K., Marsh, W., Grof, P., Munoz, R., Murray, G., Ritter, P., Lewitzka, U., Severus, E., Whybrow, P. C., & Bauer, M. (2013). Antidepressant dosage taken by patients with bipolar disorder: Factors associated with irregularity. International Journal of Bipolar Disorders, 1. https://doi.org/10.1186/2194-7511-1-26 Brath, H., Mehta, N., Savage, R. D., Gill, S. S., Wu, W., Bronskill, S. E., Zhu, L., Gurwitz, J. H., & Rochon, P. A. (2018). What Is Known About Preventing, Detecting, and Reversing	

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				Prescribing Cascades: A Scoping Review. Journal of the American Geriatrics Society, 66(11), 2079–2085. https://doi.org/10.1111/jgs.15543 Fava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151 Fava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The Deceptive Manifestations of Treatment Resistance in Depression: A New Look at the Problem. Psychotherapy and Psychosomatics, 1–9. https://doi.org/10.1159/000507227 Haahr, M. E. et al. (2014) 'Central 5-HT4receptor binding as biomarker of serotonergic tonus in humans: A [11C]SB207145 PET study', Molecular Psychiatry, 19(4), pp. 427–432. Doi: 10.1038/mp.2013.147. Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A	

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				systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029 Howes, O. D., Thase, M. E., & Pillinger, T. (2021). Treatment resistance in psychiatry: State of the art and new directions. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01200-3 Kinrys, G. et al. (2019) 'Tachyphylaxis in major depressive disorder: A review of the current state of research', Journal of Affective Disorders. Elsevier B.V., 245(October 2018), pp. 488–497. Doi: 10.1016/j.jad.2018.10.357. Meyer, J. et al. (2001) 'The Effect of Paroxetine on 5-HT2A Receptors in Depression: An [18F]Setoperone PET Imaging Study', American Journal of Psychiatry, (January), pp. 78–85. NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90	

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				O'Brien, C. P. (2018). Chapter 24: Drug Use Disorders and Addiction. In L. L. Brunton, R. Hilal-Dandan, & B. C. Knollmann (Eds.), Goodman & Gilman's The pharmacological basis of therapeutics. (13th ed.). McGraw-Hill Medical. Olver, James S., Graham D. Burrows, and Trevor R. Norman. 1999. Discontinuation Syndromes with Selective Serotonin Reuptake Inhibitors Are There Clinically Relevant Differences ? 12 (3): 171–77. Renoir, T. (2013). Selective Serotonin Reuptake Inhibitor Antidepressant Treatment Discontinuation Syndrome: A Review of the Clinical Evidence and the Possible Mechanisms Involved. Frontiers in Pharmacology, 4. https://doi.org/10.3389/fphar.2013.00045 Solomon, D. A. et al. (2005) 'Tachyphylaxis in unipolar major depressive disorder.', The Journal of clinical psychiatry. United States, 66(3), pp. 283–290. Doi: 10.4088/jcp.v66n0302.	
International	Guideline	007	013-016	We are concerned that clinicians following this recommendation (1.3.1) as written may imply	Thank you for your comment. This second bulled of this recommendation has been reworded to say 'many side

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I Institute for Psychiatric Drug Withdrawal				that drug adverse effects are inconsequential and this may be interpreted by the patient as discouraging reporting of early adverse effects. *If the medicine is an antidepressant or gabapentinoid* *− that the effect of the medicine may occur slowly and they might experience side effects before noticing any benefit* *- that any side effects are likely to ease over time.* One recent systematic review estimated "Around one in 20 patients are exposed to preventable harm in medical care" with 25% of the incidents related to drugs, but found insufficient data available for both primary care and psychiatry (Panagioti et al., 2019). A 2014 analysis of the medical records (from hospitals, outpatient clinics, and primary care) for nearly 5,000 randomly chosen Swedish individuals found "Drugs for the nervous system contributed to 43.7% of preventable ADRs (psychoanaleptics 17.8%, psycholeptics 15.6%, analgesics 14.1%), with antidepressants dominating adverse drug reactions (ADRs) (Hakkarainen et al., 2014). Some adverse drug effects upon initiation such as anxiety, jitteriness, activation, insomnia, hypomania, akathisia, serotonin toxicity, suicidality or, conversely, excessive somnolence	effects are likely to ease over time' rather than 'any'. It is not intended to discourage reporting of adverse effects, but the committee agree it is important to highlight these points, so the person knows what to expect and is not discouraged. However, the recommendations for review included in the guideline highlight that adverse effects are an important part of these reviews, including as a potential reason to increase the frequency of review or to arrange an unscheduled review. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note that most are provided for information in support of points made and therefore are descriptive articles/literature reviews rather than primary studies or systematic reviews of primary studies and are not relevant to include in any of the guideline reviews (Avery 2013, Bogowicz 2021, Cleare 2008, the Jha and Steinman papers, Carvalho 2016, Hawkins 2021, Luft 2018, Khalil 2020, Zareifopoulos 2021). The comparators in Braund 2021 did not match protocol of the relevant review on Withdrawal symptoms (review C) as this study compared antidepressants to one another, rather

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				or disorientation indicate the drug should be immediately reduced or discontinued (Carvalho et al., 2016; Hawkins, et al., 2021; Jha, et al., 2017; Luft, et al., 2018; Talton, 2020; Van Gestel, 2018; Zareifopoulos, et al., 2021. Clinicians should also be alert to physiological symptoms, such as gastrointestinal, genitourinary, sexual dysfunction, hyponatremia, skin rashes, bleeding, sweating, ophthalmic manifestations, and hyperprolactinemia, as well as such risks as liver damage (Carvalho et al., 2016). Initiation of a drug, dosage changes (including reduction), and drug changes are known to be the highest risk periods for adverse effects, requiring careful monitoring (Avery, 2013; GMC, 2021). It is the clinician's responsibility to advise the patient of this and actively closely monitor the process (Jha et al., 2018; Jha, 2019; Steinman, et al., 2011) (Figure 1), as well as instruct the patient to report suspected adverse drug effects to the MHRA (GMC, 2021). The statement made on line 16 ("that any side Effects are likely to ease over time") relies on the process of adaptation, as noted in the Context section of the NICE guidance. Adverse effects of antidepressants may often improve over time because of adaptation to the presence	than to no withdrawal or placebo as stated in the guideline review protocol. The study design of studies included in the systematic review by Panagioti 2019 did not match relevant review protocols in this guideline. The aims of Hakkarainen 2014, Talton 2020 and van Gastel 2020 were not relevant to any of the guideline review questions. Sinclair 2014 was also not relevant to include in the guideline monitoring review as it is a non-comparative cohort study, therefore not relevant to include in either the intervention or qualitative element of the monitoring reviews included in the guideline.

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				of the drug (Cleare et al., 2015) – this is evidence of tolerance and dependence. However, they do not always resolve quickly and are not always tolerable. Braund, et al., 2021 found that 8 weeks after initiating antidepressants, 11% of subjects suffered a burden of adverse effects such that they were moderately impaired to unable to function, and that this degree of burden interfered with treatment effectiveness. As written, this recommendation does not support best principles of clinical care as it communicates to clinician and patient alike that drug adverse effects are inconsequential and close monitoring may not be necessary. NICE guidance should explicitly advise clinicians to actively monitor drug changes and ask patients to report to them (and MHRA) any significant drug adverse effects, particularly those that diminish daily functioning, worsen with additional doses, or are otherwise incapacitating (GMC, 2021; Steinman, 2013). Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368	

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				Braund, T. A., Tillman, G., Palmer, D. M., Gordon, E., Rush, A. J., & Harris, A. W. F. (2021). Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: An iSPOT-D report. Translational Psychiatry, 11(1), 417. https://doi.org/10.1038/s41398-021-01533-1 Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychotherapy and Psychosomatics, 85(5), 270–288. https://doi.org/10.1159/000447034 Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093	

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				GMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf Hakkarainen, K. M., Gyllensten, H., Jönsson, A. K., Andersson Sundell, K., Petzold, M., & Hägg, S. (2014). Prevalence, nature and potential preventability of adverse drug events – a population-based medical record study of 4970 adults. British Journal of Clinical Pharmacology, 78(1), 170–183. https://doi.org/10.1111/bcp.12314 Hawkins, E. M., Coryell, W., Leung, S., Parikh, S. V., Weston, C., Nestadt, P., Nurnberger, J. I., Kaplin, A., Kumar, A., Farooqui, A. A., El-Mallakh, R. S., & For the National Network of Depression Centers Suicide Prevention Task Group. (2021). Effects of somatic treatments on suicidal ideation and completed suicides. Brain and Behavior. https://doi.org/10.1002/brb3.2381 Jha, M. K., Minhajuddin, A., South, C., Rush, A. J., & Trivedi, M. H. (2017). Worsening Anxiety,	

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				Irritability, Insomnia, or Panic Predicts Poorer Antidepressant Treatment Outcomes: Clinical Utility and Validation of the Concise Associated Symptom Tracking (CAST) Scale. International Journal of Neuropsychopharmacology, 21(4), 325–332. https://doi.org/10.1093/ijnp/pyx097 Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047 Khalil, H., & Huang, C. (2020). Adverse drug reactions in primary care: A scoping review. BMC Health Services Research, 20. https://doi.org/10.1186/s12913-019-4651-7 Luft, M. J., Lamy, M., DelBello, M. P., McNamara, R. K., & Strawn, J. R. (2018). Antidepressant-Induced Activation in Children and Adolescents: Risk, Recognition and	

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				Management. Current Problems in Pediatric and Adolescent Health Care, 48(2), 50–62. https://doi.org/10.1016/j.cppeds.2017.12.001 Panagioti, M., Khan, K., Keers, R. N., Abuzour, A., Phipps, D., Kontopantelis, E., Bower, P., Campbell, S., Haneef, R., Avery, A. J., & Ashcroft, D. M. (2019). Prevalence, severity, and nature of preventable patient harm across medical care settings: Systematic review and meta-analysis. BMJ, l4185. https://doi.org/10.1136/bmj.l4185 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. *Journal of the American Geriatrics Society*, *59*(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	

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				Talton, C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042 Van Gastel, A. (2018). Drug-Induced Insomnia and Excessive Sleepiness. Sleep Medicine Clinics, 13(2), 147–159. https://doi.org/10.1016/j.jsmc.2018.02.001 Zareifopoulos, N., Katsaraki, M., Stratos, P., Villiotou, V., Skaltsa, M., Dimitriou, A., Karveli, M., Efthimiou, P., Lagadinou, M., & Velissaris, D. (2021). Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic. European Review for Medical and Pharmacological Sciences, 25(14), 4746–4756. https://doi.org/10.26355/eurrev_202101_26386	
International Institute for Psych	Guideline	007	014	There is no evidence for this assertion on line 14 (recommendation 1.3.1): *that the effect of the medicine may occur slowly and they might experience side effects before noticing any benefit*	Thank you for your comment. This was informed by qualitative evidence identified in evidence review A. Evidence rated as high confidence, showed that people were unsure about the time taken for antidepressants to start having a therapeutic effect, and people are not aware that side effects can occur before the therapeutic effects. The review findings

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iatric Drug Withdrawal				Eventual benefit after a period of adverse effects is by no means certain. A 2009 Cochrane review found a median NNT 9 for benefit from tricyclic antidepressants and median NNT 7 for SSRIs (Arroll et al., 2009). In individual-patient meta-analyses, Hieronymous (2019) showed antidepressants do not separate from placebo at any time point at a magnitude that has been 61andomized to be clinically important (at least 3 points on the HAM-D scale). No clinically significant benefit was also found in conversion of the difficult to interpret, dichotomised 'response rate' category in Cipriani's meta-analysis into the underlying continuous symptom score (Munkholm, 2020). While adverse drug effects may be temporary, their resolution is not evidence the drug effect is beneficial. Rather, this is considered due to physiological adaptation to the drug (Cleare et al., 2015). Further, medications have effects – some adverse and some beneficial. It is misleading to frame adverse effects as 'side effects', suggesting they are somehow less important, when many, such as emotional blunting and sexual dysfunction, are more common than beneficial effects (Goodwin, et al., 2017; Serretti and Chiesa, 2009).	indicated that if people are aware of this early on, this could facilitate coping with side effects. They also noted that in their experience people being prescribed gabapentinoids can experience a time lag between the initiation of treatment and any benefits. The committee agreed it is important to emphasise the time lag between the initiation of treatment and any anticipated benefits, and that side effects may occur before the benefits. It is important not to disregard the side effects and to emphasise that these side effects are likely to settle over time. It was agreed that the time lag can vary depending on the indication for which the medicine is prescribed. This is detailed briefly in the rationale for this recommendation and in more detail in the discussion of the evidence in evidence review A. The references you have Provided have been checked for inclusion in the guideline evidence reviews. We note that these are provided for information relevant to points raised and therefore are not relevant to include, as they do not address issues relevant to the review questions in the guideline, for example due to focussing instead on efficacy or adverse effects experienced while using the medicine rather than during withdrawal.

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				As written, line 14 would mislead patients by suggesting adverse effects are infrequent and guaranteeing benefit of drug treatment – a potentially misleading promise. It might be rephrased: "that they might experience adverse effects that may be temporary" It would also be more accurate to refer to 'side effects' as 'adverse effects (often known as 'side effects).' Arroll, B., Elley, C. R., Fishman, T., Goodyear-Smith, F. A., Kenealy, T., Blashki, G., Kerse, N., & MacGillivray, S. (2009). Antidepressants versus placebo for depression in primary care. Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD007954 Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of	

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				Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093 Goodwin, G. M., Price, J., De Bodinat, C., & Laredo, J. (2017). Emotional blunting with antidepressant treatments: A survey among depressed patients. Journal of Affective Disorders, 221, 31–35. https://doi.org/10.1016/j.jad.2017.05.048 Hieronymus F, Lisinski A, Nilsson S, Eriksson E. Influence of baseline severity on the effects of SSRIs in depression: an item-based, patient-level post-hoc analysis. Lancet Psychiatry. 2019 Sep;6(9):745-752. Doi: 10.1016/S2215-0366(19)30216-0. Epub 2019 Jul 11. PMID: 31303567. Serretti, A., & Chiesa, A. (2009). Treatment-Emergent Sexual Dysfunction Related to Antidepressants: A Meta-Analysis. Journal of Clinical Psychopharmacology, 29(3). https://journals.lww.com/psychopharmacology/Fulltext/2009/06000/Treatment_Emergent_Sexual_Dysfunction_Related_to.11.aspx	

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International Institute for Psychiatric Drug Withdrawal	Guideline	008	013-016	We commend this Prescribing Strategies recommendation (1.3.5) that clinicians start with a low dose and include the patient in collaborative care. We are concerned that the follow-up process is not more concretely explained. NICE already deems regular medication reviews essential, but it has been shown prescribers are lax about following up psychotropic prescriptions (Duncan et al., 2019; Sinclair et al., 2014; Treadwell et al., 2020). Clinician complacency leading to "set and forget" after antidepressant initiation is unwarranted, often with years going by without even annual review (Sinclair et al., 2014). Braund, et al., 2021 found that 8 weeks after initiating antidepressants, 11% of subjects suffered a burden of adverse effects such that they were moderately impaired to unable to function, and that this degree of burden interfered with treatment effectiveness. By leaving the follow-up process vague, this recommendation as written does not explicitly remind clinicians of best principles of clinical care. NICE guidance should explicitly advise clinicians to initiate frequent medication reviews (Cleare, et al., 2015; Steinman et al., 2011), as well as urging patients to report to them (and	Thank you for your comment. The committee agree that a plan for follow up and review is important, and this is reflected in the recommendations. Recommendation 1.4.1 on the frequency of reviews does state that they need to be regular. This recommendation also includes a list of factors that indicate that frequent reviews will be required, including if the person is taking the medicine for the first time. Recommendation 1.4.2 states that the healthcare professional should consider increasing the frequency of reviews during dose adjustment. The committee agree it is important the review schedule is determined on the individual circumstances relevant to the person, and that required frequency would vary not only according to the medicine, but also for individuals. Therefore, they agreed it was not appropriate to recommend specific timeframes for frequency of review, but the need for regular review, with some situations requiring increased frequency, is clearly stated in the recommendations. The references you have provided have been checked for inclusion in the guideline evidence reviews but we note some are provided for information relevant to points raised and therefore due to being descriptive articles they are not relevant to include (Cleare 2008, and the Steinman papers). The comparators in Braund 2021 did not match protocol of the relevant review on Withdrawal symptoms (review C) as

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				MHRA) any significant drug adverse effects, particularly those that diminish daily functioning, worsen with additional doses, or are otherwise incapacitating (GMC, 2021; Steinman, 2013). Braund, T. A., Tillman, G., Palmer, D. M., Gordon, E., Rush, A. J., & Harris, A. W. F. (2021). Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: An iSPOT-D report. Translational Psychiatry, 11(1), 417. https://doi.org/10.1038/s41398-021-01533-1 Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093 Duncan, P., Cabral, C., McCahon, D., Guthrie, B., & Ridd, M. J. (2019). Efficiency versus thoroughness in medication review: A qualitative	this study compared antidepressants to one another, rather than to no withdrawal or placebo as stated in the guideline review protocol. Sinclair 2014 did not meet the protocol criteria for the monitoring review as it is a non-comparative cohort study, therefore not relevant to either the intervention or qualitative element of the monitoring reviews included in the guideline. The study by Duncan 2019 does not address the objectives of the guideline monitoring review and therefore is not relevant to include. Treadwell 2021 also did not meet the objectives of any of the guideline review questions.

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				interview study in UK primary care. British Journal of General Practice, 69(680), e190–e198. https://doi.org/10.3399/bjgp19X701321 GMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf Sinclair, J. E., Aucott, L. S., Lawton, K., Reid, I. C., & Cameron, I. M. (2014). The monitoring of longer term prescriptions of antidepressants: Observational study in a primary care setting. Family Practice, 31(4), 419–426. https://doi.org/10.1093/fampra/cmu019 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and	

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				non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965 Treadwell, J. S., Wong, G., Milburn-Curtis, C., Feakins, B., & Greenhalgh, T. (2020). GPs' understanding of the benefits and harms of treatments for long-term conditions: An online survey. BJGP Open, bjgpopen20X101016. https://doi.org/10.3399/bjgpopen20X101016	
International Institute for Psychiatric Drug Withdrawal	Guideline	008	005-006	We are concerned that this recommendation (1.3.4) does not emphasize close monitoring during the initiation phase or dosage changes of a drug of dependence. NICE already deems regular medication reviews essential, but it has been shown prescribers are lax about recognizing the risks and monitoring for adverse effects of psychotropics (Duncan et al., 2019; Sinclair et al., 2014; Treadwell et al., 2020), not being aware these drugs require a novel style of clinical attention. Historically, the long-term prescribing of drugs of dependence has not been not central to primary care. The last 20 years have seen a tremendous change in GP psychotropic prescribing patterns.	Thank you for your comment. Recommendations for review are included in section 1.4. Recommendation 1.4.1 on the frequency of reviews does state that they need to be regular. This recommendation also includes a list of factors that indicate that frequent reviews will be required, including if the person is taking the medicine for the first time. Recommendation 1.4.2 states that the healthcare professional should consider increasing the frequency of reviews during dose adjustment. The committee agree it is important the review schedule is determined on the individual circumstances relevant to the person, and that required frequency would vary not only according to the medicine, but also for individuals. Therefore, they agreed it was not appropriate to recommend specific timeframes for frequency of review, but the need for regular review, with some

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				A recent analysis of all English NHS primary care prescription of antidepressants found a tripling of such GP activity, even after accounting for population growth, from 18.4 million items in 1998 to 70.9 million in 2018 (Bogowicz et al., 2021). Psychiatric treatment now occupies a great deal of primary care practice. Public Health England recently estimated 17% of the British adult population takes antidepressants, with 26% of the adult population having been dispensed any prescribed drug of dependence in 2017-2018 (Public Health England, 2020). A 2018 Mind UK study that polled1,066 GPs found "GPs estimate that 4 in 10 (41 per cent) of their consultations now involve a mental health element". One way or the other, GPs will need to care for many patients taking drugs of dependence. Hedenrud et al., 2013 found Swedish GPs quite perplexed about and wanting training in mental health prescribing and pharmacology. With their unusually wide range of individualized effect, psychotropics require close monitoring during initiation or drug changes to address serious adverse effects as soon as possible (Avery et al, 2015, Cleare et al., 2015; Jha et al., 2018; Jha, 2019; Steinman, 2013) (Figure 1).	situations requiring increased frequency, is clearly stated in the recommendations. The references you have provided have also been checked for inclusion in the guideline evidence reviews. We note most are provided for information relevant to points raised and therefore are descriptive articles or non-systematic reviews and therefore not relevant to include (Avery 2013, Bogowicz 2021, Cleare 2008, the Jha and Steinman papers, Carvalho 2016, Zareifopoulos 2021). The comparators in Braund 2021 did not match protocol of the relevant review on Withdrawal symptoms (review C) as this study compared antidepressants to one another, rather than to no withdrawal or placebo as stated in the guideline review protocol. Sinclair 2014 did not meet the protocol criteria for the monitoring review as it is a non-comparative cohort study, therefore not relevant to either the intervention or qualitative element of the monitoring reviews included in the guideline. The studies by Duncan 2019 Hedenrud 2013 do not address the objectives of the guideline monitoring review and therefore are not relevant to include. Treadwell 2021 also did not meet the objectives of any of the guideline review questions.

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				Some adverse drug effects upon initiation such as anxiety, jitteriness, activation, insomnia, hypomania, akathisia, serotonin toxicity, suicidality or, conversely, excessive somnolence or disorientation indicate the drug should be immediately reduced or discontinued (Carvalho et al., 2016; Hawkins, et al., 2021; Jha, et al., 2017; Luft, et al., 2018; Talton, 2020; Van Gestel, 2018; Zareifopoulos, et al., 2021. Clinicians should also be alert to physiological symptoms, such as gastrointestinal, genitourinary, sexual dysfunction, hyponatremia, skin rashes, bleeding, sweating, ophthalmic manifestations, and hyperprolactinemia, as well as such risks as liver damage (Carvalho et al., 2016). Clinician complacency leading to "set and forget" after antidepressant initiation is unwarranted, often with years going by without even annual review (Sinclair et al., 2014). Braund, et al., 2021 found that 8 weeks after initiating antidepressants, 11% of subjects suffered a burden of adverse effects such that they were moderately impaired to unable to function, and that this degree of burden interfered with treatment effectiveness. Initiation of a drug, dosage changes (including reduction), and drug changes are known to be	

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				the highest risk periods for adverse effects, requiring careful monitoring (Avery, 2013; GMC, 2021). It is the clinician's responsibility to advise the patient of this, as well as instruct the patient to report suspected adverse drug effects to the MHRA (GMC, 2021). As it leaves the follow-up process vague, this recommendation as written does not explicitly remind clinicians of best principles of clinical care. NICE guidance regarding drugs of dependence should explicitly advise clinicians to initiate frequent medication reviews (Steinman et al., 2011) and encourage collaborative care (Cleare et al., 2015; Steinman, 2013), asking patients to report to them (and MHRA) any significant drug adverse effects, particularly those that diminish daily functioning, worsen with additional doses, or are otherwise Incapacitating (GMC, 2021; Steinman, 2013). Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368 Bogowicz, P., Curtis, H. J., Walker, A. J., Cowen, P., Geddes, J., & Goldacre, B. (2021). Trends and variation in antidepressant	

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				prescribing in English primary care: A retrospective longitudinal study. BJGP Open, 5(4), BJGPO.2021.0020. https://doi.org/10.3399/BJGPO.2021.0020 Braund, T. A., Tillman, G., Palmer, D. M., Gordon, E., Rush, A. J., & Harris, A. W. F. (2021). Antidepressant side effects and their impact on treatment outcome in people with major depressive disorder: An iSPOT-D report. Translational Psychiatry, 11(1), 417. https://doi.org/10.1038/s41398-021-01533-1 Carvalho, A. F., Sharma, M. S., Brunoni, A. R., Vieta, E., & Fava, G. A. (2016). The Safety, Tolerability and Risks Associated with the Use of Newer Generation Antidepressant Drugs: A Critical Review of the Literature. Psychotherapy and Psychosomatics, 85(5), 270–288. https://doi.org/10.1159/000447034 Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating	

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				depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093 Duncan, P., Cabral, C., McCahon, D., Guthrie, B., & Ridd, M. J. (2019). Efficiency versus thoroughness in medication review: A qualitative interview study in UK primary care. British Journal of General Practice, 69(680), e190–e198. https://doi.org/10.3399/bjgp19X701321 GMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf Hawkins, E. M., Coryell, W., Leung, S., Parikh, S. V., Weston, C., Nestadt, P., Nurnberger, J. I., Kaplin, A., Kumar, A., Farooqui, A. A., El-Mallakh, R. S., & For the National Network of Depression Centers Suicide Prevention Task Group. (2021). Effects of somatic treatments on suicidal ideation and completed suicides. Brain and Behavior. https://doi.org/10.1002/brb3.2381	

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				Hedenrud, T. M., Svensson, S. A., & Wallerstedt, S. M. (2013). "Psychiatry is not a science like others"—A focus group study on psychotropic prescribing in primary care. BMC Family Practice, 14(1), 115. https://doi.org/10.1186/1471-2296-14-115 Jha, M. K., Minhajuddin, A., South, C., Rush, A. J., & Trivedi, M. H. (2017). Worsening Anxiety, Irritability, Insomnia, or Panic Predicts Poorer Antidepressant Treatment Outcomes: Clinical Utility and Validation of the Concise Associated Symptom Tracking (CAST) Scale. International Journal of Neuropsychopharmacology, 21(4), 325–332. https://doi.org/10.1093/ijnp/pyx097 Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047	

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				Luft, M. J., Lamy, M., DelBello, M. P., McNamara, R. K., & Strawn, J. R. (2018). Antidepressant-Induced Activation in Children and Adolescents: Risk, Recognition and Management. Current Problems in Pediatric and Adolescent Health Care, 48(2), 50–62. https://doi.org/10.1016/j.cppeds.2017.12.001 Mind UK. (2018). GP mental health training survey Summary. Mind.org.uk. https://www.mind.org.uk/media-a/4414/gp-mh-2018-survey-summary.pdf Public Health England. (2020, December 3). Prescribed medicines review: Summary. GOV.UK. https://www.gov.uk/government/publications/prescribed-medicines-review-report/prescribed-medicines-review-summary Sinclair, J. E., Aucott, L. S., Lawton, K., Reid, I. C., & Cameron, I. M. (2014). The monitoring of longer term prescriptions of antidepressants: Observational study in a primary care setting. Family Practice, 31(4), 419–426. https://doi.org/10.1093/fampra/cmu019	

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				Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and adverse drug events in older adults. Journal of the American Geriatrics Society, 59(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Talton, C. W. (2020). Serotonin Syndrome/Serotonin Toxicity. Federal Practitioner: For the Health Care Professionals of the VA, DoD, and PHS, 37(10), 452–459. https://doi.org/10.12788/fp.0042 Treadwell, J. S., Wong, G., Milburn-Curtis, C., Feakins, B., & Greenhalgh, T. (2020). GPs' understanding of the benefits and harms of treatments for long-term conditions: An online survey. BJGP Open, bjgpopen20X101016. https://doi.org/10.3399/bjgpopen20X101016	

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				Van Gastel, A. (2018). Drug-Induced Insomnia and Excessive Sleepiness. Sleep Medicine Clinics, 13(2), 147–159. https://doi.org/10.1016/j.jsmc.2018.02.001 Zareifopoulos, N., Katsaraki, M., Stratos, P., Villiotou, V., Skaltsa, M., Dimitriou, A., Karveli, M., Efthimiou, P., Lagadinou, M., & Velissaris, D. (2021). Pathophysiology and management of Akathisia 70 years after the introduction of the chlorpromazine, the first antipsychotic. European Review for Medical and Pharmacological Sciences, 25(14), 4746–4756. https://doi.org/10.26355/eurrev_202101_26386	
International Institute for Psychiatric Drug Withdrawal	Guideline	008	010-011	We are concerned that this recommendation (1.3.4) suggests drug dosage increases are an expected outcome of psychotropic medication reviews. Although this is common practice, British Association for Psychopharmacology guidelines (Cleare et al., 2015) found it is supported only by custom, not by evidence when it comes to antidepressants specifically: A systematic review found no consistent evidence for increased efficacy after dose escalation in nonresponders compared with continuing lower doses for SSRIs in seven	Thank you for your comment. This recommendation has been reworded to say, 'check whether the dose needs to be adjusted and, if so, how to do this safely.' So, it does not separate increase or decrease in dose. An additional statement has also been added to recommendation 1.3.8 in the prescribing strategies section to clarify that if a satisfactory response to a medicine is achieved but subsequently lost, this may be for a number of reasons

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				RCTs, but in most studies the timing of dose increase was rather early (3–6 weeks) (Adli et al., 2005). Three large77andomizedd double-blind studies found that raising the dose of sertraline and fluoxetine has no benefit over staying on the original dose (Dornseif et al., 1989, Licht and Qvitzau, 2002; Schweizer et al., 2001). Indeed, the Licht and Qvitzan study reported that raising the dose of sertraline in non-responders at 6 weeks from 100 mg to 200 mg a day under77andomizedd double-blind conditions had a significantly poorer outcome than staying on the lower dose. As higher doses are associated with a greater risk of adverse events and discontinuation effects, raising the dose of these drugs may increase the risk without the benefit of better efficacy (Cleare et al., 2015). There are major factors for non-response to drug treatment that cannot be remedied by increasing drug dosage. Ho et al., 2016 estimated about 50% of patients may not adhere to regular drug schedules, experiencing adverse effects, such as withdrawal symptoms, which may cause the patient to report non-response to the current drug dosage. Misdiagnosis is	including tolerance, and in that circumstance medicines should not be automatically escalated. The references you have provided have been checked for inclusion in our evidence reviews those provided for information relevant to points raised are not relevant to include due to being descriptive articles (Cleare 2008, Malhi 2019). The aim and PICO of systematic review by Ho did not match of the guideline review objectives as it focusses on efficacy. Studies included in the systematic review also did not match the review objectives.

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				another contributor to reported non-response (Cleare, 2015; Malhi et al., 2019), as the patient may have received inappropriate treatment to begin with. Increase in dosage should not be automatic for non-response or any patient complaint. For the sake of patient safety, NICE guidance should state increase in drug dosage should be undertaken only when reasons for non-response, such as lack of a true psychiatric condition or non-adherence to a regular drug schedule, have been ruled out, and risk of increased adverse drug effects due to dosage increase is low. Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093	

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				Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029 Malhi, G. S., Das, P., Mannie, Z., & Irwin, L. (2019). Treatment-resistant depression: Problematic illness or a problem in our approach? British Journal of Psychiatry, 214(1), 1–3. https://doi.org/10.1192/bjp.2018.246	
International Institute for Psychiatric Drug Withdrawal	Guideline	011	021-029	We are concerned that this recommendation (1.4.5) does not remind the clinician to check for irregular dosing when patients report a change in their condition or a change in symptom pattern. Such irregularities may be the patient accidentally taking extra doses, skipping a dose, or taking drugs off-schedule. Drugs of dependence require a novel type of clinical attention. Within weeks, patients taking these drugs regularly will become neurobiologically adapted to them (physiologically dependent, as explained in the	Thank you for your comment. Although the committee agree this is an important factor in a review of prescribed medicines, they agreed that medicines adherence issues apply to all medicines and are not specific to those related to dependence and withdrawal symptoms that are included within these guidelines. Recommendation 1.4.4 cross refers to both the NICE Medicines adherence and Medicines optimisation guideline which cover this for all prescribed medicines. A statement has also been included in recommendation 1.3.1 on the information that should be given to people when

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				guidance's Context). As acknowledged in NICE CG90 Stopping antidepressants. Draft for consultation, November 2021, they will be at high risk of unpleasant withdrawal symptoms if they accidentally forget doses, skip them, or take them off-schedule (Meijer et al., 2001; NICE, 2021). These withdrawal symptoms may be mistaken by the patient or clinician as intensifying symptoms of the original complaint or a medical condition, occasioning the expense and risk of inappropriate medical care and prescription escalation (Demyttenaere & Haddad, 2000; Ho et al., 2016). Non-adherence can also lead to treatment resistance or iatrogenic pseudo-resistance (Fava et al., 2020; Howes et al., 2021). The neurobiological basis for the adverse effects of irregular dosing of psychotropics is explained in Horowitz & Taylor, 2022 and Sørensen et al., 2021 in their discussions of changes in receptor occupancy and drug plasma saturation in relation to dosing changes. Departures from a regular dosing schedule would not be a rare occurrence among patients. Estimates for patient non-adherence to antidepressants run as high as 50% (Ho et al., 2016). This type of patient behavior is also common with other psychiatric drugs, with	starting a medicine to highlight to the person that missing doses may lead to symptoms of withdrawal. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note many are provided for information relevant to points raised and are therefore descriptive articles/literature reviews or conceptual analyses rather than primary studies or systematic reviews of primary studies and so are not relevant to include (e.g., Demyttenaere 2000, Fava 2020, Howes 2021) Meijer 2001 did not meet the protocol criteria for the monitoring review as it is a non-comparative cohort study, therefore not relevant to either the intervention or qualitative element of the monitoring reviews included in the guideline. Ho 2016, Semahegn 2020 and Sørensen 2021 are systematic reviews the aim and PICO of which did not match any of the guideline review questions. Horowitz and Taylor 2022 will not be published till February 2022; however, it appears to be a descriptive article that would therefore not meet the study inclusion criteria for the relevant review questions.

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				adverse drug effects being a common patient motivation for missing doses; lack of clinician follow-up is a key factor in patient non-adherence (Semahegn et al., 2020). As written, this recommendation is incomplete and may lead to clinical error. Following the lead of NICE, 2021, clinicians should be advised symptom changes may result from patients failing to take their drugs on a consistent daily schedule, taking the drugs inconsistently may cause unpleasant symptoms due to physiological dependency and withdrawal, and they should inquire about irregularity in dosing whenever assessing the progress of the patient's treatment. Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093	

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				Demyttenaere, K., & Haddad, P. (2000). Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 101(s403), 50–56. https://doi.org/10.1111/j.1600-0447.2000.tb10948.x Fava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The Deceptive Manifestations of Treatment Resistance in Depression: A New Look at the Problem. Psychotherapy and Psychosomatics, 1–9. https://doi.org/10.1159/0005072277 Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029 Horowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001	

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				Howes, O. D., Thase, M. E., & Pillinger, T. (2021). Treatment resistance in psychiatry: State of the art and new directions. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01200-3 Meijer, W. E. E., Bouvy, M. L., Heerdink, E. R., Urquhart, J., & Leufkens, H. G. M. (2001). Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. British Journal of Psychiatry, 179(6), 519–522. https://doi.org/10.1192/bjp.179.6.519 NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90 Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020). Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: A systematic review and meta-analysis. Systematic Reviews, 9. https://doi.org/10.1186/s13643-020-1274-3	

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				Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-w Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	
International Institute for Psychiatric Drug Withdrawal	Guideline	011	024-027	We are concerned that this recommendation (1.4.5) perpetuates a misunderstanding of dependence, confounding physiological dependence and addiction (O'Brien, 2011), inconsistent with the correct definition earlier provided in Context. It presents examples, taken from addiction medicine, of drug-seeking behavior not applicable to most people taking prescription psychotropics. All people using these psychoactive drugs regularly will develop some degree of dependence. This does not mean they will demonstrate behaviors of addiction. They do not need to be running out of	Thank you for your comment. The context section has been reworded to clarify the definitions of dependence and addiction, as well as problems associated with dependence, which is used in the guideline recommendations. The recommendations also now clarify that dependence is an expected phenomenon of these medicines but that some people may experience problems associated with dependence. Recommendation 1.4.5 refers to the problems associated with dependence (not dependence itself), which the committee believe is appropriate and consistent with the definitions provided in the context, now this section has been

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				a medication early, making frequent requests for dose increases – these examples of drug-seeking behavior are likely to lead doctors to miss the fact that all patients using these drug classes regularly will becoming physiologically dependent on their medication. Studies show that doses of antidepressants may gradually escalate over years, which is a common outcome of physiological adaptation leading to tolerance, not drug-seeking. A systematic review found that loss of drug effect, termed tachyphylaxis (the clinical consequence of tolerance), occurred in 9% to 57% of patients with depression treated with antidepressants (Kinrys et al., 2019). In one longitudinal study it was observed that 25% of patients required increased dosages of antidepressant over time (Solomon et al., 2005), consistent with the development of tolerance. Meanwhile, the recommendation does not address other problems associated with physiological dependence that are more germane to primary care, such as interdose or rebound withdrawal symptoms (common with opioids, benzodiazepines, gabapentinoids, and Z-drugs) (Allison & Pratt, 2003; Lerner & Klein, 2019) or emotional blunting (common with all psychotropics) (Goodwin et al., 2017; Guina &	clarified. The committee agree that is important all of the factors stated in the recommendation are considered in a review of medicines associated with dependence and withdrawal symptoms. This recommendation (as all in the guideline) should be applied alongside clinical judgement, and other condition specific NICE guidelines, to determine the most appropriate course of action, in a shared decision with the person. The references you have provided have been checked for inclusion in our evidence reviews. We note most are provided for information relevant to points raised and are therefore are descriptive articles/literature reviews rather than primary studies or systematic reviews of primary studies not directly relevant to objectives of the guideline review protocols, which do not meet the guideline protocol inclusion criteria. The committee are aware of the Ashton manual this is acknowledged in the committee's discussion of the evidence in evidence review C (Safe withdrawal).

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				Merrill, 2018; Szmulewicz et al., 2016), which may be mistaken for symptoms of the original complaint or treatment resistance and lead to misdiagnosis and overprescription (Brath et al., 2018). As written, this recommendation is misleading and incomplete and may cause clinicians to fail to inquire about and address common adverse consequences of long-term psychotropic prescription. Allison, C., & Pratt, J. A. (2003). Neuroadaptive processes in GABAergic and glutamatergic systems in benzodiazepine dependence. Pharmacology & Therapeutics, 98(2), 171–195. https://doi.org/10.1016/S0163-7258(03)00029-9 Ashton, C. H. (2002). Benzodiazepines: How They Work & How to Withdraw (The Ashton Manual). Benzodiazepine Information Coalition. https://www.amazon.com/Benzodiazepines-They-Withdraw-Ashton-Manual-ebook/dp/B07QGNP9BL Brath, H., Mehta, N., Savage, R. D., Gill, S. S., Wu, W., Bronskill, S. E., Zhu, L., Gurwitz, J. H., & Rochon, P. A. (2018). What Is Known About Preventing, Detecting, and Reversing Prescribing Cascades: A Scoping Review.	

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				Journal of the American Geriatrics Society, 66(11), 2079–2085. https://doi.org/10.1111/jgs.15543 Goodwin, G. M., Price, J., De Bodinat, C., & Laredo, J. (2017). Emotional blunting with antidepressant treatments: A survey among depressed patients. Journal of Affective Disorders, 221, 31–35. https://doi.org/10.1016/j.jad.2017.05.048 Guina, J., & Merrill, B. (2018). Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. Journal of Clinical Medicine, 7(2), E17. https://doi.org/10.3390/jcm7020017 Kinrys, G. et al. (2019) 'Tachyphylaxis in major depressive disorder: A review of the current state of research', Journal of Affective Disorders. Elsevier B.V., 245(October 2018), pp. 488–497. doi: 10.1016/j.jad.2018.10.357. Lerner, A., & Klein, M. (2019). Dependence, withdrawal and rebound of CNS drugs: An update and regulatory considerations for new drugs development. Brain Communications, 1(1). https://doi.org/10.1093/braincomms/fcz025	

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				O'Brien, C. (2011) 'Addiction and dependence in DSM-V', Addiction (Abingdon, England). 2010/10/06, 106(5), pp. 866–867. doi: 10.1111/j.1360-0443.2010.03144.x. Solomon, D. A. et al. (2005) 'Tachyphylaxis in unipolar major depressive disorder.', The Journal of clinical psychiatry. United States, 66(3), pp. 283–290. doi: 10.4088/jcp.v66n0302. Szmulewicz, A., Samamé, C., Caravotta, P., Martino, D. J., Igoa, A., Hidalgo-Mazzei, D., Colom, F., & Strejilevich, S. A. (2016). Behavioral and emotional adverse events of drugs frequently used in the treatment of bipolar disorders: Clinical and theoretical implications. International Journal of Bipolar Disorders, 4(1), 6. https://doi.org/10.1186/s40345-016-0047-3	
International Institute for Psychiatric	Guideline	013	018-022	Although this advice (1.5.7) is well meaning and intuitively rational, this recommendation could be harmful and is not supported by an evidence base: *more rapid withdrawal of a medicine that is causing significant harm (the speed of rapid*	Thank you for your comment. The committee note that rapid withdrawal is not the recommended approach in most cases, however, this think it is very important this is included in the cases where there is significant harm. Recommendation 1.5.6 includes examples of these exceptional circumstances. The rationale for the recommendation states that this is

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Drug Withdrawal				*withdrawal depends on the type of medicine and the person's circumstances)* Even in the case when a medication is causing significant harm, rapid withdrawal may cause even greater harm. (Guy et al., 2020) contains case studies of patients who are long-term disabled by abruptly stopping these drugs, which should give pause to consideration of this course of action. The FDA addressed this issue in a 2019 bulletin, to reduce harm to patients whose physicians, alarmed by the opioid epidemic, were discontinuing their prescriptions too precipitously, causing cases of severe opioid withdrawal. The FDA's urging of gradual taper was accompanied by a Guide for Clinicians (HHS, 2019), supported by an article in the New England Journal of Medicine (Dowell et al., 2019). This is the catch-22 of these drugs associated with dependence and withdrawal – even when using is harmful, stopping too quickly can cause even greater harm. Clinicians should be well aware of this. We would recommend that even in the case of significant harm that reduction is gradual (if perhaps slightly quicker than it would be if there were no harm). Perhaps this statement could be more balanced and refer to	usually done in a hospital setting as the committee acknowledge for some medicines this will require extra care. The references you have provided have been checked for inclusion in the guideline evidence reviews but being descriptive articles or grey literature rather than primary studies or systematic review of primary studies, they do not meet the guideline prespecified protocol inclusion criteria.

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				"balancing the risk of ongoing use of the medication against too rapid withdrawal of the medication." Dowell, D., Haegerich, T., & Chou, R. (2019). No Shortcuts to Safer Opioid Prescribing. The New England Journal of Medicine, 380(24), 2285–2287. https://doi.org/10.1056/NEJMp1904190 FDA. (2019). FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering (FDA Drug Safety Communication) [Safety Announcement]. FDA Center for Drug Evaluation and Research (CDER). http://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes Guy, A. et al. (2020) 'The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition', Therapeutic Advances in Psychopharmacology. SAGE Publications Ltd STM, 10, p. 204512532096718. doi: 10.1177/2045125320967183.	

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				HHS. (2019). HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics. U.S. Department of Health and Human Services. https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf	
International Institute for Psychiatric Drug Withdrawal	Guideline	013	026-027	We are concerned that this guidance document in its entirety contains no information to help clinicians decide on which drug to taper first, as required in this advice (1.5.7). *which medicines to reduce first, if the person will be withdrawing from more than 1 medicine* Unfortunately, many patients are concurrently taking multiple drugs of dependence, a complex problem in psychiatric treatment (Fava & Rafanelli, 2019). General practitioners find polypharmacy difficult to manage (Anthierens et al., 2010). The field of deprescribing has suggested guidelines for deciding which drug to taper first (Scott et al., 2015), as well as patient advocates (Framer, 2021). We strongly urge the committee include clinician guidance specifically in decision-making	Thank you for your comment. An evidence review was not included to address priorities of medicine reduction if more than one was being tapered. The committee's view is that it is not always appropriate to follow a scientific rationale for which medicine should be reduced first without considering the person's individual circumstances and preferences. As well as this the decision would depend on the individual circumstances and the balance of benefits and harms, including signs that the person was developing problems with dependence relevant to the medicines the person was taking. The references you have provided have been have also been checked for inclusion in our evidence reviews however, the study designs or study details do not meet the protocols for inclusion. Descriptive articles/literature reviews are not included (Fava 2019, Framer 2021, Scott 205). Anthierens 2010 does not meet protocol criteria for any of the qualitative reviews undertaken due to the study population, or the aim of the study.

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				regarding how to reduce the burden of multiple drugs of dependence with informed, systematic deprescribing methods. Anthierens, S., Tansens, A., Petrovic, M., & Christiaens, T. (2010). Qualitative insights into general practitioners views on polypharmacy. BMC Family Practice, 11, 65. https://doi.org/10.1186/1471-2296-11-65 Fava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151 Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274 Scott, I. A., Hilmer, S. N., Reeve, E., Potter, K., Le Couteur, D., Rigby, D., Gnjidic, D., Del Mar, C. B., Roughead, E. E., Page, A., Jansen, J., & Martin, J. H. (2015). Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Internal Medicine, 175(5), 827–834.	

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				https://doi.org/10.1001/jamainternmed.2015.0324	
International Institute for Psychiatric Drug Withdrawal	Guideline	014	018-029	This guidance (1.5.9) appears to be incomplete. Without specific withdrawal symptoms mentioned, GPs will not be informed about this and will not in turn be able to inform their patients. There are symptoms common across all these drug classes that could be specified (Lerner & Klein, 2019). Alternatively, it would not be onerous to list common withdrawal symptoms for each drug class. There are several authoritative summaries of symptoms across these drug classes (and others are available); Chouinard & Chouinard, 2015 is one example. The physiological signs of withdrawal, such as nausea and "brain zaps" or "electrical zaps", are fairly easy to identify (Chouinard & Chouinard, 2015; Papp & Onton, 2018). When physiological symptoms are present, even if they are accompanied by psychological symptoms, the balance of probabilities would allow conclusions that the person is in a withdrawal state. One specific point – the sentence on lines 25-26:	Thank you for your comment. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person

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				withdrawal symptoms…can be physical or psychological might be mis-interpreted to suggest that withdrawal symptoms might be physical or psychological *in origin,* whereas a more accurate phrasing would specify that "withdrawal symptoms can be physical or psychological *in expression*". All withdrawal symptoms are physiological in origin (Hyman and Nestler, 1996; Lerner and Klein, 2019), with nocebo withdrawal effects from patients stopping placebo or continuing medications affecting a small proportion of patients, and likely to be more mild. What causes the most confusion for doctors are psychological or emotional withdrawal symptoms, such anxiety, depressed mood, and insomnia, because these are so easily mistaken for a return of the underlying condition. Since these symptoms cause pervasive confounding of withdrawal with "relapse", it would be important for the guidance to specify these as neurobiogically induced in order to raise medical awareness of them. Otherwise, patients are likely to be misdiagnosed as having relapsed and restarted on unnecessary medication (Haddad & Anderson, 2007).	so that they are aware and contact a healthcare professional as necessary. Regarding your point about the use of the term 'psychological', this has been reworded to state that they can affect both physical and mental health. The references you have provided have also been checked for inclusion in the guideline evidence reviews. Papp & Onton 2018 was included in the qualitative element of evidence review D on Withdrawal symptoms. The APPG report by Guy was considered for inclusion in evidence review D but did not meet the guideline protocol criteria due to being grey literature. Other studies are descriptive reviews of literature and so do not meet the guideline protocol inclusion criteria for study design (Chouinard 2015, Lerner 2019, Haddad 2007, Hyman 1996).

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				We note in the NICE draft guidance for CG90 on Depression that the following passage is included: "1.4.17 If a person has withdrawal symptoms when they stop taking antidepressant medication or reduce their dose, reassure them that they are not having a relapse of their depression. Explain that: -these symptoms are common -relapse does not usually happen as soon as you stop taking an antidepressant medication or lower the dose -even if they start taking an antidepressant medication again or increase their dose, the withdrawal symptoms may take a few days to disappear." It would be very helpful for patients and clinicians to have a similar statement included in this guideline so as to prevent patients (and clinicians) from mis-interpreting withdrawal as relapse. Substitution of antidepressant for 'drugs of dependence' and 'depression' for underlying condition would make this applicable to this guideline. As above, it would be useful to specify that these withdrawal symptoms can include psychological symptoms such as depressed mood, anxiety, trouble sleeping for all the	

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				categories of drugs included here, which are very commonly mis-interpreted as relapse of an underlying condition (or onset of a new mental health condition). This would prevent much of the mis-diagnosis commonly reported by patients (Guy et al. 2020) Chouinard, G., & Chouinard, V.-A. (2015). New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. Psychotherapy and Psychosomatics, 84(2), 63–71. https://doi.org/10.1159/000371865 Guy, A. et al. (2020) 'The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition', Therapeutic Advances in Psychopharmacology. SAGE Publications Ltd STM, 10, p. 204512532096718. doi: 10.1177/2045125320967183. Haddad, P. M., & Anderson, I. M. (2007). Recognising and managing antidepressant discontinuation symptoms. Advances in Psychiatric Treatment, 13(6), 447–457. https://doi.org/10.1192/apt.bp.105.001966	

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				Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. doi: 10.1007/s00340-005-2128-3. Lerner, A., & Klein, M. (2019). Dependence, withdrawal and rebound of CNS drugs: An update and regulatory considerations for new drugs development. Brain Communications, 1(1). https://doi.org/10.1093/braincomms/fcz025 Papp, A., & Onton, J. A. (2018). Brain Zaps: An Underappreciated Symptom of Antidepressant Discontinuation. The Primary Care Companion for CNS Disorders, 20(6). https://doi.org/10.4088/PCC.18m02311	
International Institute for Psychiatric Drug Withdrawal	Guideline	014	014	The guidance (1.5.8) contains this direction for clinicians that will leave them in a quandary: *explain how the withdrawal will be carried out* This will be an impossible task for clinicians as, based on this guidance as a whole, there is no specific guidance on how to conduct a taper – admittedly a gap in the field for more than 30 years (Leeuwen et al., 2021). Given the lack of guidance doctors are likely to fall back on the	Thank you for your comment. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to

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				plan to reduce dose by half for a month and then stop the medication. There is not enough detail in this guidance to advise them how to conduct this process in a step by step manner. If the principles of a gradual reduction in a hyperbolic manner, such as in (Horowitz & Taylor, 2019 and Horowitz & Taylor, 2022, are recommended, then there should be some guidance of how to implement them even in the absence of RCTs. What does gradual mean? And how would a GP turn the word 'hyperbolic' into a tapering schedule? Without specific guidance, they will be unable to do so and as a consequence this is likely to severely curtail the ability of this guidance to be implemented or affect change in practice. Unfortunately, as written, this guidance is incomplete and vague, and may have the unintended effect of reinforcing the status quo rather than move forward in drug discontinuation advice. Horowitz, M. A., & Taylor, D. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The Lancet Psychiatry, 6(6), 538–546. https://doi.org/10.1016/S2215-0366(19)30032-X Horowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication.	the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendation for opioids, benzodiazepines, Z-drugs and antidepressants does describe what hyperbolic tapering means in practice, but the recommendation enables flexibility in approach, and does not imply that dose reduction always has to follow a predefined trajectory, as that may not always be the most clinically appropriate approach for the person. The term hyperbolic has not been used for this reason, and as highlighted in your comment because that would not guide a GP into a tapering schedule. The committee agree that the description provided in the recommendations would be clearer to healthcare professionals. The references you have provided have been assessed for inclusion in the guideline evidence reviews. The Cochrane review by Leeuwen et al. published in April 2021 was identified in the guideline searches and assessed for inclusion. However, as the protocol of Leeuwen et al. did not match the guideline review protocol for safe withdrawal as they included studies with a comparison group that was maintained on antidepressants. Therefore the Cochrane review could not be included without amendments. Included studies were cross-checked for inclusion, however, as the publication date was after the guideline review had been undertaken, those relevant had already been included in the evidence review (for example Eveleigh 2018, Khan 2014,

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				European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001 Leeuwen, E. van, van Driel, M., De Sutter, A., Robertson, L., Kendrick, T., Horowitz, M., Donald, M., & Christiaens, T. (2021). Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults (Review). Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD013495.pub2	Segall 2010). Section 1.2.1.2 in evidence review C has been edited to reflect this. Horowitz and Taylor 2019 does not directly address the objective in the relevant review question and does not meet the study design criteria. Horowitz and Taylor will not be published until February 2022; but appears to be a descriptive article that would also not meet inclusion criteria for the relevant review.
International Institute for Psychiatric Drug Withdrawal	Guideline	015	005-027	A clear caution should be added to this guideline (5 Dose reduction) as a whole: clinicians should not advise alternating dosages or skipping doses as a tapering method. While skipping doses may seem a convenient way to "average" dosage decreases in tapering, it is also unfortunately highly effective at evoking withdrawal symptoms. There is no scientific basis for this common clinical advice and is contrary to what science knows about the dangers of inconsistent dosing, drug half-life, and the pharmacology of drugs of dependence	Thank you for your comment. The committee do not agree that this should be recommended against. They do not specifically recommend this in the guideline, but their view is that there are some circumstances when this is an appropriate way to manage dose reduction. The references you have provided have been checked for inclusion in the guideline evidence reviews. Gallahger 2012 was included in evidence review C (Safe Withdrawal). However, most papers are provided for information relevant to points made and are descriptive articles/literature reviews or conceptual analyses rather than primary studies or systematic reviews of primary studies, therefore do not meet

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				(Kaplan, 1997; Osterberg et al., 2010; Reidenberg, 2011). As an outcome of neurobiological adaptation to and physiological dependence on a regular drug dosage, unpleasant symptoms of withdrawal are evoked when that "expected" dosage is not supplied (Peper, 2004), the body struggling to maintain homeostasis (Osterberg et al., 2010). This may be most easily understood with antidepressants as an example: irregular dosing can cause fluctuations of receptor occupancy (Horowitz and Taylor, 2022) and, more immediately, drug plasma saturation, particularly with short half-life drugs (Sørensen et al., 2021), which in fact are associated with more frequent reports of withdrawal syndrome (Quilichini et al., 2022). The November, 2021 draft of NICE CG90 Stopping antidepressants directs clinicians to *Advise people taking antidepressant medication that if they stop taking it abruptly, miss doses or do not take a full dose, they may have withdrawal symptoms…. (NICE, 2021)* Just as patients are at high risk of unpleasant withdrawal symptoms if they accidentally forget doses, skip them, or take them off-schedule (Demyttenaere & Haddad, 2000; Ho et al., 2016;	the guideline review protocol criteria (Demyttenaere et al. 2000, Framer 2021, Groot & van Os 2020, Howes 2021, Kaplan 1997, Osterberg et al. 2010, Peper 2004, Reidenberg 2011). Some do not meet the protocol of the relevant review questions due to being non-comparative cohorts (Groot et al. 2021, Meijer 2001) or case studies (Stockmann 2019). Others do not address objectives relevant to the guideline review questions (Amsterdam et al. 2016, Ho et al. 2016, Sørensen et al. 2021). Quilichini et al. 2022 and Horowitz and Taylor 2022 were published after the search cut-off date for this guideline (the latter will not be published till February 2022); however, Quilichini is a case control study and Horowitz and Taylor appears to be a descriptive article that would therefore not meet the study inclusion criteria for the relevant review questions.

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				Kaplan, 1997; Meijer et al., 2001; NICE, 2021), skipping doses or alternating dosages to taper triggers even worse symptoms as the irregular dosing continues. Like non-adherence, irregular dosing as a tapering method can also lead to adverse reactions or iatrogenic pseudo-resistance should a drug regimen be restored (Amsterdam et al., 2016; Fava et al., 2020; Howes et al., 2021). Psychiatrists, clinicians, and patient experts by experience have observed the adverse effects of skipping doses as a tapering technique (Framer, 2021; Gallagher et al., 2012; Stockmann, 2019). By utilizing dosage ranges, tablet-splitting, liquid preparations (recommended in NICE 2021), and custom compounded doses (such as tapering strips, described by Groot and van Os, 2020 and Groot and Groot and van Os, 2021), there is no reason for clinicians to put their patients at risk of withdrawal by recommending skipping doses to taper. NICE should specifically and emphatically advise clinicians not to recommend or employ skipping or alternating dosages to taper drugs of dependence. The exception to this rule may be drugs with very long half-lives, of which the only pertinent example in the drugs in this guidance is fluoxetine which because of the 7-15 days half-life of the active metabolite	

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				norfluoxetine might be dosed up to as infrequently as every sixth day without serious consequence. We therefore suggest that the following advice is included: " Patients should not be advised to skip doses to taper (e.g. every other day dosing) for medications without long half-lives, as fluctuations in receptor occupancy or drug plasma level can cause severe withdrawal symptoms. Fluoxetine has a half-life long enough to allow for dosing as infrequently as up to every sixth day." Amsterdam, J. D., Lorenzo-Luaces, L., & DeRubeis, R. J. (2016). Step-wise loss of antidepressant effectiveness with repeated antidepressant trials in bipolar II depression. Bipolar Disorders, 18(7), 563–570. https://doi.org/10.1111/bdi.12442 Demyttenaere, K., & Haddad, P. (2000). Compliance with antidepressant therapy and antidepressant discontinuation symptoms. Acta Psychiatrica Scandinavica, 101(s403), 50–56. https://doi.org/10.1111/j.1600-0447.2000.tb10948.x	

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				Fava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The Deceptive Manifestations of Treatment Resistance in Depression: A New Look at the Problem. Psychotherapy and Psychosomatics, 1–9. https://doi.org/10.1159/000507227 Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274 Gallagher JC, Strzinek RA, Cheng RJ, et al. The effect of dose titration and dose tapering on the tolerability of desvenlafaxine in women with vasomotor symptoms associated with menopause. J Womens Health 2002 2012; 21: 188–198. Groot, Peter C., and Jim van Os. 2020. "How User Knowledge of Psychotropic Drug Withdrawal Resulted in the Development of Person-Specific Tapering Medication." Therapeutic Advances in Psychopharmacology 10 (January): 204512532093245.	

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				Groot, P. C., & van Os, J. (2021). Successful use of tapering strips for hyperbolic reduction of antidepressant dose: A cohort study. Therapeutic Advances in Psychopharmacology, 11, 20451253211039330. https://doi.org/10.1177/20451253211039327 Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029 Horowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001 Howes, O. D., Thase, M. E., & Pillinger, T. (2021). Treatment resistance in psychiatry: State of the art and new directions. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01200-3 Kaplan EM. Antidepressant noncompliance as a factor in the discontinuation syndrome. J Clin	

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				Psychiatry 1997; 58 Suppl 7: 31–35; discussion 36. Meijer WEE, Bouvy ML, Heerdink ER, et al. Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. Br J Psychiatry 2001; 179: 519–522. NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90 Osterberg, L. G., Urquhart, J., & Blaschke, T. F. (2010). Understanding Forgiveness: Minding and Mining the Gaps Between Pharmacokinetics and Therapeutics. Clinical Pharmacology & Therapeutics, 88(4), 457–459. https://doi.org/10.1038/clpt.2010.171 Peper, A. (2004). A theory of drug tolerance and dependence I: A conceptual analysis. Journal of Theoretical Biology, 229(4), 477–490. https://doi.org/10.1016/j.jtbi.2004.04.010	

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				Reidenberg, M. M. (2011). Drug Discontinuation Effects Are Part of the Pharmacology of a Drug. The Journal of Pharmacology and Experimental Therapeutics, 339(2), 324–328. https://doi.org/10.1124/jpet.111.183285 Sørensen, A., Ruhé, H. G., & Munkholm, K. (2021). The relationship between dose and serotonin transporter occupancy of antidepressants—A systematic review. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01285-w Stockmann T. What it was like to stop an antidepressant. Ther Adv Psychopharmacol 2019; 9: 2045125319884834. Quilichini, J.-B., Revet, A., Garcia, P., Bouquié, R., Hamard, J., Yrondi, A., & Montastruc, F. (2022). Comparative effects of 15 antidepressants on the risk of withdrawal syndrome: A real-world study using the WHO pharmacovigilance database. Journal of Affective Disorders, 297, 189–193. https://doi.org/10.1016/j.jad.2021.10.041	

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International Institute for Psychiatric Drug Withdrawal	Guideline	015	007-017	This advice (1.5.10) is incomplete and unclear. There is no specification as to what a 'slow, stepwise rate of reduction proportionate to the existing dose' entails. Without examples, clinicians will not be able to implement this advice. Even including some broad guidelines or examples such as in the Benzodiazepine NICE CKS, or in the BNF chapter on Hypnotics and Anxiolytics would make it much more likely that this important recommendation is implemented in practice. The absence of such guidance may mean that practice is not changed from the status quo. The inclusion of several examples similar to the following (from the the Benzodiazepine NICE CKS at https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/management/benzodiazepine-z-drug-withdrawal/) would make the difference between a guideline that could be implemented and one that is well meaning but too vague to affect any real change in practice. **"Suggested withdrawal schedule for diazepam** From diazepam 40 mg per day or less: Reduce dose by 2–4 mg every 1–2 weeks until reaching 20 mg per day, then	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. The committee consider that the recommendations do describe a schedule that a healthcare professional can follow, but also allows flexibility in approach, and does not imply that dose reduction always has to follow a predefined trajectory, as that may not always be the most clinically appropriate approach for the person. An additional recommendation has been added to acknowledge use of published withdrawal schedules but notes that if used these should be applied flexibly. The references you have provided have been checked for inclusion in the guideline evidence reviews. However, most papers are provided for information relevant to points made and are descriptive articles/literature reviews or conceptual analyses rather than primary studies or systematic reviews of primary studies, therefore do not meet the guideline review protocol criteria (Horowitz & Taylor 2019, Groot and van Os, 2020, Davies et al 2021, Fava & Rafanelli, 2019; Framer, 2021)

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				Reduce dose by 1–2 mg every 1–2 weeks until reaching 10 mg per day, then Reduce dose by 1 mg every 1–2 weeks until reaching 5 mg per day, then Reduce dose by 0.5–1 mg every 1–2 weeks until completely stopped. Estimated total withdrawal time: From diazepam 40 mg per day: 30–60 weeks. From diazepam 20 mg per day: 20–40 weeks." Similar guidelines could be developed for medications addressed in this guideline: the pattern of dose reduction given above for diazepam is very similar in pattern for any medication addressed when aiming to conform to pharmacological principles (with a similar pattern extrapolated for doses above 40mg) – whether from the opioid, antidepressant, benzodiazepine, z-drug or gabapentinoid (see below) class. All these drug classes show a hyperbolic pattern between dose of drug and effect on target receptors (including clinical effects) (Horowitz and Taylor, 2019, Horowitz and Taylor, 2022) and so the same pattern of dose reductions as applies to diazepam (with its hyperbolic relationship to GABA-A occupancy). A suggested broad scheme is provided below.	Or due to being non-randomised cohort studies (e.g., Groot 2021) they are not eligible for inclusion as sufficient RCT evidence was available for the relevant evidence review on Safe withdrawal. Others do not address objectives relevant to the guideline review questions (Amsterdam et al. 2016). Horowitz and Taylor 2022 will not be published till February 2022; however, it appears to be a descriptive article that would therefore not meet the study inclusion criteria for the relevant review questions. Personal communications cannot be considered as evidence to inform guidelines for the NHS.

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				There are several examples of such guidelines available in the current edition of the Maudsley Prescribing Guidelines, as well as in the appendices of this article: Horowitz, M. A. and Taylor, D. (2019) 'Tapering of SSRI treatment to mitigate withdrawal symptoms', The Lancet Psychiatry. Elsevier Ltd, 6(6), pp. 538–546. doi: 10.1016/S2215-0366(19)30032-X. Another way to provide practical guidance that could be implemented by clinicians would be to simply provide a range of reduction schedules that captures most patients. For example, the guidance could say, in a similar manner to the specifications for proportional dose reductions made in the draft NICE CG90 depression guideline (although the rate of reduction recommended in the CG90 draft guideline will be rather too quick for most patients): "Many patients report that they can only reduce by 10% of their most recent dose every 2 to 4 weeks (so that the reductions become smaller and smaller as the total dose gets lower). Some patients may be able to reduce by larger amounts, up to 25% or 50% every two to four week (so that reductions become smaller and smaller as the total	

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				dose gets lower) and some patients will need to reduce by even smaller portions than 10% a month. The different rates of reductions that may be tolerated by a patient may be related to past experience of withdrawal effects, type of medication, and duration of use. The best way to determine this rate is to make a test reduction and monitor the patient's response in order to titrate further reductions to a rate that is tolerable for the patient. If uncomfortable withdrawal symptoms occur, maintain the current dose until symptoms lessen (or increase the dose level back to where withdrawal symptoms were not present) and thereafter reduce at a more gradual rate. For patients on these medications for a few weeks, only a few weeks should be required for tapering, but for those taking drugs of dependence for longer periods, tapering over many months and sometimes years may be required to ensure the process is tolerable. The dose can be reduced to zero when the reduction to zero from this dose does not cause a greater reduction in receptor	

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				occupancy (i.e. effect on the brain) than previous reductions that were tolerable. For some patients this will mean reducing to 1mg or less of a medication before stopping it." Another option, similar to the current form on the NICE Benzodiazepine CKS would be include general guidance that is able to be implemented. For example, the following: "For medications that are usually dosed at >500mg · Reduce dose by 100–500 mg every 2–4 weeks until reaching 500 mg per day, then · Reduce dose by 10–50 mg every 2–4 weeks until reaching 100 mg per day, then · Reduce dose by 2–10 mg every 2–4 weeks until reaching 20 mg per day, then · Reduce dose by 1-2 mg every 2–4 weeks until completely stopped. For medications that are usually dosed at 100 to 500mg · Reduce dose by 10–50 mg every 2–4 weeks until reaching 100 mg per day, then · Reduce dose by 2–10 mg every 2–4 weeks until reaching 20 mg per day, then	

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				· Reduce dose by 0.5-2 mg every 2–4 weeks until reaching 5 mg per day, then · Reduce dose by 0.5-1 mg every 2–4 weeks until completely stopped. For medications that are usually dosed at <100mg · Reduce dose by 2–10 mg every 2–4 weeks until reaching 20 mg per day, then · Reduce dose by 0.5-2 mg every 2–4 weeks until reaching 5 mg per day, then · Reduce dose by 0.2-0.5 mg every 2–4 weeks until reaching 2mg a day, then · Reduce dose by 0.1-0.4 mg every 2–4 weeks until completely stopped. " Variations on this guidance could be made to refer to specific drugs or drug classes. This would have the advantage of providing clinicians with clear guidance on how to reduce medications and follows the pharmacological pattern for drug effects as well as similar guidance for benzodiazepines in other NICE publications. Another practical barrier to implementing proportional tapers for many of the medications covered in this guideline is limited dosage forms (Horowitz and Taylor, 2019; Groot and van Os, 2020; Groot and van Os, 2021). Without explicit	

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				direction for clinicians, many will consider any recommended tapering process impossible to incorporate into practice. For example, reduction of a dose of 20mg of citalopram by 25% will require making 15mg by splitting a 20mg tablet into quarters with a tablet cutter. A subsequent reduction by 25%, to 11.25mg, will require a liquid version of the drug as it will be impossible to make this amount using available tablet formulations. Liquid formulations are supplied by the manufacturers of many of the common drugs covered by this guideline. NICE CG90 Stopping antidepressants. Draft for consultation, November 2021 endorses the use of liquid preparations for tapering ("use liquid preparations if necessary to allow slow tapering, once small doses have been reached", p.16, lines 11-12). (The tapering rate recommendation in the draft CG90 will be rather too quick for most patients). A similar explicit recommendation that liquid preparations of the medications will be useful for tapering in practice would be a vital addition to this guideline – as a counter to the culture in GP practices of avoiding liquid preparations because of the sometimes increased cost burden (in the short-term). This increased cost burden could also be set against the amount of	

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				money spent by the NHS on unnecessary medications covered in this guideline (Davies et al., 2021). Custom compounded capsules can also provide dosages intermediate between available tablet formulations as well as much smaller for the later phase of a taper. Tapering strips, commissioned by a not- for-profit foundation in the Netherlands, are partially mass-produced packets of monthly doses tailored, by a prescriber, to the tapering requirements of the patient. The medication in the tapering strips is approved for prescription in the Netherlands for a nationally determined, regulated fee. Signed by 11,414 UK residents, a petition, Provide Tapering Strips for People Who Want to Withdraw Safely from Psychotropic Drugs, was presented in 2019 to Secretary of State for Health and Social Care Matt Hancock (J. Moore, personal communication, September 10, 2019). In support of the petition, Professor Wendy Burn, then president of the Royal College of Psychiatrists, wrote to Mr. Hancock: "…NICE guidelines say that a person choosing to stop taking antidepressants should withdraw gradually, but there are currently no "off-the-shelf' solutions for withdrawal. This complements the Royal	

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				College of Psychiatrists call for 'NICE to develop clear evidence-based and pharmacologically-informed recommendations to help guide gradual withdrawal from antidepressant use' in its recently published position statement on antidepressants and depression. We therefore support the proposal to pilot a trial of antidepressant tapering strips in a sample of GP surgeries and/or psychiatric clinics and would support a national roll-out should the evidence demonstrate better results for patients. (W. Burn, personal communication, October 7, 2019)" We suggest the addition of the following practical information to the current draft document about safe prescribing and withdrawal management for adults: "In order to facilitate a proportionate reduction of these drug classes, the use of tablet cutters to divide tablets into smaller doses and liquid versions of medications (either as solutions prepared by manufacturers or dispersible forms that can be made into suspensions) can be useful. 'Tapering strips' or other tablets compounded to make up smaller dose	

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				formulations may also facilitate the process." It is common in the process of tapering off one of these drugs that, when unpleasant withdrawal symptoms arise, a doctor will recommend that the patient start another one of these medications – for example, the addition of a benzodiazepine or an antipsychotic at low dose -- which leads to the patient then being dependent on another drug associated with dependence or withdrawal. In our experience (psychiatrists, clinicians, and patient experts by experience), this generally leads to worse problems as patients in withdrawal from psychiatric drugs often become sensitised to additional medications (Amsterdam et al., 2016; Fava & Rafanelli, 2019; Framer, 2021). We suggest this proviso be included: "The addition of beta-blockers, antipsychotics and other drugs associated with dependence and withdrawal should be avoided where possible. If intolerable withdrawal symptoms arise, it is better to pause the reduction or make a small increase back on the drug being tapered" Amsterdam, J. D., Lorenzo-Luaces, L., & DeRubeis, R. J. (2016). Step-wise loss of antidepressant effectiveness with repeated	

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				antidepressant trials in bipolar II depression. Bipolar Disorders, 18(7), 563–570. https://doi.org/10.1111/bdi.12442 Burn, W. (2019, October 7). Letter to Rt Hon Matt Hancock MP [Personal communication]. Davies, J., R. E. Cooper, J. Moncrieff, L. Montagu, T. Rae, and M. Parhi. 2021. "The Costs Incurred by the NHS in England due to the Unnecessary Prescribing of Dependency-Forming Medications." *Addictive Behaviors*, 107143. Fava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151 Framer, Adele. 2021. "What I Have Learnt from Helping Thousands of People Taper Off Psychotropic Medications." Therapeutic Advances in Psychopharmacology 11 (January): 204512532199127. Groot, Peter C., and Jim van Os. 2020. "How User Knowledge of Psychotropic Drug Withdrawal Resulted in the Development of	

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				Person-Specific Tapering Medication." Therapeutic Advances in Psychopharmacology 10 (January): 204512532093245. Groot, P. C., & van Os, J. (2021). Successful use of tapering strips for hyperbolic reduction of antidepressant dose: A cohort study. Therapeutic Advances in Psychopharmacology, 11, 20451253211039330. https://doi.org/10.1177/20451253211039327 Horowitz, Mark Abie, and David Taylor. 2019. "Tapering of SSRI Treatment to Mitigate Withdrawal Symptoms." The Lancet Psychiatry 6 (6): 538–46. Horowitz, M. A., & Taylor, D. (2022). How to reduce and stop psychiatric medication. European Neuropsychopharmacology, 55, 4–7. https://doi.org/10.1016/j.euroneuro.2021.10.001 Moore, J. (2019, September 10). Letter to Rt Hon Matt Hancock MP: Tackling Prescribed Drug Dependence and Withdrawal [Personal communication].	

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				NICE. (2021). CG90 Stopping antidepressants. Draft for consultation, November 2021. In Depression in adults: Recognition and management. National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/cg90 NICE Clinical Knowledge Summaries. (2019). Benzodiazepine and z-drug withdrawal. NICE. https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/management/benzodiazepine-z-drug-withdrawal/ Taylor, D., Barnes, T. R. E., & Young, A. H. (2021). The Maudsley Prescribing Guidelines in Psychiatry (14th edition). Wiley.	
International Institute for Psychiatric Drug Withdrawal	Guideline	015	013	As written, this guidance (1.5.10) is incomplete and unclear, failing to resolve the central question of tapering technique for clinicians. *ensure that the rate of reduction is likely to be tolerable for the person* In order to enable a clinician to ensure that the rate of reduction is tolerable for patients, they will need further detail about how to implement a tolerable taper. For example, patients should be	Thank you for your comment. The committee do not agree that a healthcare professional would not be able to determine a tolerable rate of reduction for the person. All recommendations should be applied with the healthcare professional's clinical knowledge and

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				given regular assessment of withdrawal symptoms (such as measuring using a tool like the Discontinuation Emergent Signs and Symptoms (DESS) daily or twice weekly) (Jha, 2019) and clinical guidance provided on how to modify a withdrawal schedule accordingly (Framer, 2021; Jha et al., 2018), such as "- Mild withdrawal symptoms suggest continue the taper after symptom resolution. - Withdrawal symptoms of moderate severity suggesting pausing the taper to allow symptoms to resolve, and thereafter pursing a more gradual reduction. - Severe withdrawal symptoms indicate patients should increase their dose and stabilize for some time before attempting a more gradual reduction." Our above suggestion is aligned with similar wording in the NICE CG90 Stopping antidepressants. Draft for consultation, November 2021 (NICE, 2021). The addition of this slight amount of detail will furnish clinicians with a much better understanding of how to monitor and adjust tapering of these medications. The absence of clarity in this guidance might prevent these guidelines from being implemented adequately	expertise, which in the committee's view would enable them to effectively apply these recommendations to practice. The recommendation has been slightly reworded to state that they should ensure the schedule is acceptable to the person, and to explain that the reduction schedule can may be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. However, the committee agree that a healthcare professional would have the ability to modify the withdrawal schedule as appropriate in discussion with the person. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note some are provided for information relevant to points raised and are therefore being descriptive articles/literature reviews and are not relevant to include in the reviews (Framer 2021 & Jha 2018). However, the information summarised within those papers (including the difficulty to distinguish between relapse and discontinuation symptoms, the variability in the duration of withdrawal symptoms) has been captured by the evidence included in the guideline, and reflected in the recommendations made. The APPG report by Guy et al. was considered for inclusion in evidence review D (Withdrawal symptoms) but did not

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				and reducing the harm produced for some patients (Guy et al., 2020). Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274 Guy, A. et al. (2020) 'The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition', Therapeutic Advances in Psychopharmacology. SAGE Publications Ltd STM, 10, p. 204512532096718. doi: 10.1177/2045125320967183. Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of	meet the guideline protocol criteria due to being grey literature.

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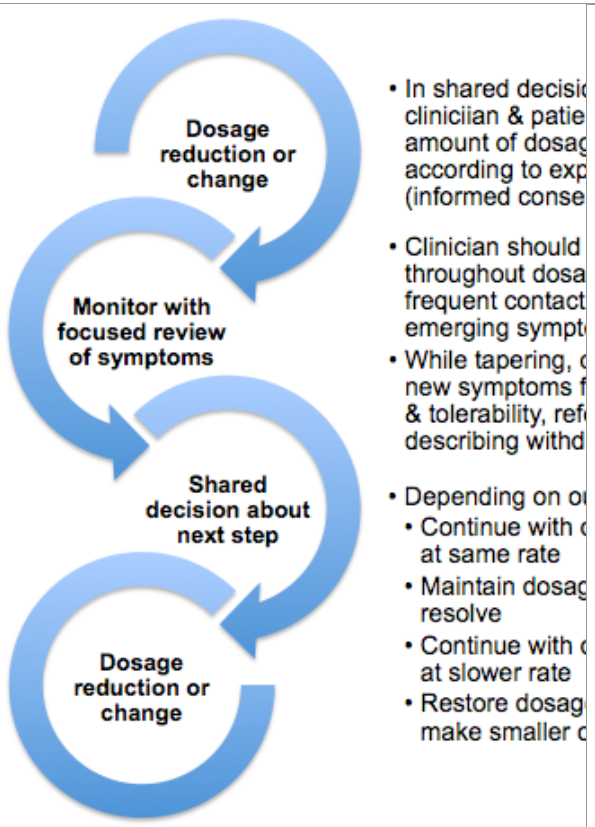
				Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047	
International Institute for Psychiatric Drug Withdrawal	Guideline	015	018	As written, this guidance is not sufficiently specific about monitoring during tapering. Initiation of a drug, dosage changes (including reduction), and drug changes are known to be the highest risk periods for adverse effects (Avery, 2013; GMC, 2021). It is the clinician's responsibility to advise the patient of this as well as actively closely monitor the process (Jha et al., 2018; Jha, 2019; Steinman, 2013; Steinman, et al., 2011) (Figure 1). We suggest that the phrase "*agree regular intervals for reviewing the reduction schedule*" be modified to say "agree on regular and frequent intervals for reviewing the reduction schedule" as this process can be difficult to navigate without frequent monitoring. The process can be visualized as shown in Figure 1.	Thank you for your comment. The committee agree that monitoring of dose reduction is important. As well as references to review in this section, the recommendations in section 1.4 on monitoring also apply here, including 1.4.2 which highlights that more frequent reviews may be required during dose adjustments. The committee agree this should be discussed with the person, but consider this is already covered within the recommendations. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note that they are provided for information relevant to points raised and therefore are descriptive articles/literature reviews which are not relevant to include in the evidence reviews (Avery 2013, Jha 2018, 2019, Steinman 2011, 2013). However, the information summarised within those papers (including the importance of shared decision making, the difficulty to distinguish between relapse and discontinuation symptoms, the variability in the duration of withdrawal symptoms) has been captured by the evidence included in the guideline, and is reflected in the recommendations.

				 Figure 1. Process of dosage reduction or change with shared dec monitoring. After Jha et al., 2018 and Jha, 2019	

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				Avery, T., Gookey, G., Spencer, R., Knox, R., Marsden, K., & Salema, N. (2013). Providing the right medication monitoring. InnovAiT: Education and Inspiration for General Practice, 6(8), 515–523. https://doi.org/10.1177/1755738013494368 GMC. (2021). Good practice in prescribing and managing medicines and devices. In Ethical guidance for doctors. General Medical Council. https://www.gmc-uk.org/-/media/documents/prescribing-guidance-updated-english-20210405_pdf-85260533.pdf Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Jha, M. K. (2019). Discontinuing Antidepressants: How Can Clinicians Guide Patients and Drive Research? The Journal of Clinical Psychiatry, 80(6), 0–0. https://doi.org/10.4088/JCP.19com13047 Steinman, M. A., Handler, S. M., Gurwitz, J. H., Schiff, G. D., & Covinsky, K. E. (2011). Beyond the prescription: Medication monitoring and	

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				adverse drug events in older adults. *Journal of the American Geriatrics Society*, *59*(8), 1513–1520. https://doi.org/10.1111/j.1532-5415.2011.03500.x Steinman, M. A. (2013). Reaching out to patients to identify adverse drug reactions and non-adherence: Necessary but not sufficient. JAMA Internal Medicine, 173(5), 375–394. https://doi.org/10.1001/jamainternmed.2013.2965	
International Institute for Psychiatric Drug Withdrawal	Guideline	016	019-022	We are concerned that this guidance (1.5.16) might suggest to clinicians that the psychological symptoms of withdrawal are relapse or that withdrawal itself is primarily psychosomatic. Further, the offer of support is restricted to benzodiazepines and to group cognitive behavioural therapy (CBT), among all psychotherapeutic methods that may be available. First, it should be understood that though RCTs are lacking (as they are for all adverse treatment effects), the single most effective way to support withdrawal is to allow people to taper more gradually over a longer period, as shown in observational studies (Murata et al., 2010; Groot	Thank you for your comment. The recommendation to consider CBT was informed by clinical evidence suggesting this may be beneficial for some people in terms of improving cessation and reduction of benzodiazepine use, relapse rate as well as improving quality of life and by an economic model demonstrating it to be cost effective in improving cessation rate, and quality of life. While some evidence did suggest there was also an improvement of withdrawal symptoms, this was not the main factor informing the recommendation. The recommendation has therefore now been amended to remove the statement 'to support people to manage symptoms. This recommendation does not state that it is for relapse prevention, nor does the rationale for this recommendation. The committee therefore does not agree that it implies that

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				and van Os, 2021; Horowitz and Taylor, 2019) and our experience, as psychiatrists, clinicians and patient experts by experience, in tapering patients off drugs of dependence (Framer, 2021; Horowitz and Taylor, 2019). Second, while this recommendation may be derived from studies of benzodiazepine withdrawal, any patient experiencing withdrawal from any drug of dependence may benefit from psychotherapeutic support, which may help them cope with symptoms as they slowly recover from withdrawal. CBT is known to be effective for some types of symptoms but not all types of symptoms. People experiencing psychotropic withdrawal should not be expected to control the symptoms of neurological upset or unbearable physiological withdrawal symptoms with mindfulness or reframing, or discouraged that they have reverted to their original psychiatric condition. They should be supported by therapists specifically trained in the vicissitudes of withdrawal (Guy, et al., 2019). Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in	symptoms of withdrawal are relapse. The committee agree it is important to recommend something where evidence demonstrates that it may help some people. They agree that evidence on other interventions was lacking to inform recommendations and other approaches may also be beneficial, and also that the evidence and recommendation are specific to benzodiazepines. The committee agreed that there were limitations in the evidence and so this recommendation is worded as 'consider'. They also noted because of these limitations and the limited evidence across medicine classes that it would not be appropriate to extrapolate this evidence to other medicines and so a number of research recommendations were included both for other medicines and other interventions to support withdrawal. The recommendations do already include stating that dose reduction should be done slowly, and may take several months or more. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note some are provided as information relevant to points raised and are therefore descriptive articles/literature reviews not relevant to include in the evidence reviews (Framer 2021). Groot 2021 et al. is an uncontrolled cohort study and therefore not relevant to include in the review for Safe

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				Psychopharmacology. https://doi.org/10.1177/2045125321991274 Groot, Peter C., and Jim van Os. 2021. "Successful Use of Tapering Strips for Hyperbolic Reduction of Antidepressant Dose: A Cohort Study." *Therapeutic Advances in Psychopharmacology* 11: 204512532110393. Guy, Anne, James Davies, and Rosemary Rizq. 2019. *Guidance for Psychological Therapists: Enabling Conversations with Clients Taking or Withdrawing from Prescribed Psychiatric Drugs*. London: APPG for Prescribed Drug Dependence. Horowitz, M. A. and Taylor, D. (2019) 'Tapering of SSRI treatment to mitigate withdrawal symptoms', The Lancet Psychiatry. Elsevier Ltd, 6(6), pp. 538–546. doi: 10.1016/S2215-0366(19)30032-X. Murata, Yusuke, Daisuke Kobayashi, Nanae Imuta, Koichi Haraguchi, Ichiro Ieiri, Ryoji Nishimura, Susumu Koyama, and Kazunori Mine. 2010. "Effects of the Serotonin 1A, 2A, 2C, 3A, and 3B and Serotonin Transporter Gene Polymorphisms on the Occurrence of Paroxetine	withdrawal. Neither Murata 2010 or Horowitz & Taylor 2019 directly address the objectives of the relevant review question and do not meet the study design inclusion criteria for the review question. The APPG report by Guy et al. was considered for inclusion in evidence review D (Withdrawal symptoms) but did not meet the review protocol study design inclusion criteria due to being grey literature.

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				Discontinuation Syndrome." *Journal of Clinical Psychopharmacology* 30 (1): 11–17.	
International Institute for Psychiatric Drug Withdrawal	Guideline	016	15-018	We are concerned that by recommending psychological interventions for relapse prevention, this guidance (1.5.15) might suggest to clinicians that the psychological manifestations of withdrawal are relapse or that withdrawal itself is primarily psychosomatic. While patients may appreciate and learn from psychotherapeutic support, which may help them cope with symptoms as they slowly recover from withdrawal, they should not be misled that they have reverted to their original psychiatric condition by being treated as such. They should be supported by therapists specifically trained in the vicissitudes of withdrawal (Guy, et al., 2019). Guy, A., Davies, J., & Rizq, R. (2019). Guidance for Psychological Therapists: Enabling conversations with clients taking or withdrawing from prescribed psychiatric drugs. APPG for Prescribed Drug Dependence. https://prescribeddrug.info/guidance-for-psychological-therapists/	Thank you for your comment. The recommendation to consider CBT was informed by clinical evidence suggesting this may be beneficial for some people in terms of improving cessation and reduction of benzodiazepine use, relapse rate as well as improving quality of life and by an economic model demonstrating it to be cost effective in improving cessation rate, and quality of life. While some evidence did suggest there was also an improvement of withdrawal symptoms, this was not the main factor informing the recommendation. The recommendation has therefore now been amended to remove the statement 'to support people to manage symptoms. This recommendation does not state that it is for relapse prevention, nor does the rationale for this recommendation. The committee therefore does not agree that it implies that symptoms of withdrawal are relapse.The committee agrees it is important to recommend something where evidence demonstrates that it may help some people. They agree that evidence on other interventions was lacking to inform recommendations and other approaches may also be beneficial, and also that the evidence and recommendation are specific to benzodiazepines. The committee agreed that there were limitations in the evidence and so this

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					recommendation is worded as 'consider'. They also noted because of these limitations and the limited evidence across medicine classes that it would not be appropriate to extrapolate this evidence to other medicines and so a number of research recommendations were included both for other medicines and other interventions to support withdrawal. The APPG report by Guy et al. was considered for inclusion in evidence review D (Withdrawal symptoms) but did not meet the review protocol study design inclusion criteria.
International Institute for Psychiatric Drug Withdrawal	Guideline	016	010-012	In addition to the sensible advice in this guideline (1.5.15), clinicians need more guidance about distinguishing withdrawal symptoms from a re-emergence of prior mental symptoms. First, clinicians need to understand that withdrawal symptoms have a temporal connection to dosage reductions (or inconsistent dosing) in that they often, but not always, appear within a week after the dosage change (Chouinard & Chouinard, 2015; (Jha et al., 2018). Then, they need to understand the many easy-to-identify physiological symptoms of withdrawal, such as nausea and "brain zaps" or "electrical	Thank you for your comment. The committee's view is that the information provided in the recommendation about distinguishing withdrawal symptoms from re-emergence of the original symptoms reinforces this message and will help healthcare professionals to distinguish these. For the reasons already stated, the committee do not agree that a list of withdrawal symptoms can be provided within this guideline. One risk of doing so would be that new symptoms could be overlooked which would be detrimental to someone's healthcare. The references you have provided have been checked for inclusion in the guideline evidence reviews. Papp & Onton 2018 has been included in the qualitative element of evidence review D on Withdrawal symptoms.

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				zaps" (Chouinard & Chouinard, 2015; Lerner and Klein, 2019; Papp & Onton, 2018). When physiological symptoms are present, even if they are accompanied by psychological symptoms, in all probability the person is likely to be in a withdrawal state. What causes the most confusion for doctors are psychological or emotional withdrawal symptoms, such anxiety, depressed mood, and insomnia, because these are so easily mistaken for a return of the underlying condition. But again, the temporal relationship to dosage change, a novel presentation, or co-occurring physiological withdrawal symptoms would indicate the source is withdrawal (Chouinard & Chouinard, 2015). It is important for guidelines to explain this or patients are highly likely to be misdiagnosed as having relapsed and restarted on unnecessary medication (Haddad & Anderson, 2007). Chouinard, G., & Chouinard, V.-A. (2015). New Classification of Selective Serotonin Reuptake Inhibitor Withdrawal. Psychotherapy and Psychosomatics, 84(2), 63–71. https://doi.org/10.1159/000371865 Haddad, P. M., & Anderson, I. M. (2007). Recognising and managing antidepressant	Chouinard 2015, Jha 2018, Lerner 2019 are descriptive literature reviews and so do not meet the guideline prespecified protocol inclusion criteria for the relevant review. However, the information summarised within these papers including the difficulty to distinguish between relapse and discontinuation symptoms, the variability in the duration of withdrawal symptoms has been captured by the evidence included in the present guideline, and is reflected in the recommendations.

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				discontinuation symptoms. Advances in Psychiatric Treatment, 13(6), 447–457. https://doi.org/10.1192/apt.bp.105.001966 Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692 Lerner, A., & Klein, M. (2019). Dependence, withdrawal and rebound of CNS drugs: An update and regulatory considerations for new drugs development. Brain Communications, 1(1). https://doi.org/10.1093/braincomms/fcz025 Papp, A., & Onton, J. A. (2018). Brain Zaps: An Underappreciated Symptom of Antidepressant Discontinuation. The Primary Care Companion for CNS Disorders, 20(6). https://doi.org/10.4088/PCC.18m02311	
International Institute for	Guideline	016	013-014	This guidance (1.5.15) should be more specific. It should also be added that if such withdrawal symptoms have occurred, this indicates the reduction schedule is too fast for the individual. Any subsequent reductions should be made at a	Thank you for your comment. The recommendation already states that this should be a prompt to consider delaying the next dose reduction or reverting to the previous dose. 'Trying

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Psychiatric Drug Withdrawal				more gradual pace (i.e. smaller decrements of dose and/or longer periods between reductions) (Framer, 2021; Horowitz and Taylor, 2019; Jha et al., 2018). If the same reduction schedule is resumed, the same problems with withdrawal will be encountered. Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274 Horowitz, M. A. and Taylor, D. (2019) 'Tapering of SSRI treatment to mitigate withdrawal symptoms', The Lancet Psychiatry. Elsevier Ltd, 6(6), pp. 538–546. doi: 10.1016/S2215-0366(19)30032-X. Jha, M. K., Rush, A. J., & Trivedi, M. H. (2018). When Discontinuing SSRI Antidepressants Is a Challenge: Management Tips. The American Journal of Psychiatry, 175(12), 1176–1184. https://doi.org/10.1176/appi.ajp.2018.18060692	a smaller dose reduction' has now also been added to the recommendation. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note these are provided as information relevant to the points made, and are therefore descriptive articles/literature reviews that are not relevant to include in the relevant reviews (Framer 2021, Horowitz 2019, Jha 2018). However, the information summarised within those papers (including the difficulty to distinguish between relapse and discontinuation symptoms, the variability in the duration of withdrawal symptoms) has been captured by the evidence included in the present guideline, and is reflected in the recommendations.

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APPG for Prescribed Drug Dependence	Guideline	General	General	This guideline provides much useful guidance in relation to safe prescribing. However, it does not provide enough detail on slow tapering to support safe withdrawal from drugs of dependence. For example, it provides no information on tapering rates, time between dose reductions, how to reduce doses or overall duration of taper. This means that doctors and patients will be unable to use the information in this guidance in order to withdraw from these drugs safely, and as such it is not currently fit for purpose. We note that the evidence review does not include any review of the published articles or studies on hyperbolic tapering, which is a method for safe tapering. While there are no RCTs on hyperbolic tapering, it has been developed by patients and patient groups over many years, and there are several relevant studies. These are included below. In addition, charities, researchers and patient groups could provide testimony to the NICE committee of the effectiveness of this approach. We also note that the BNF and NICE Clinical Knowledge Summaries provide more information on slow tapering, as well as the	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendation for opioids, benzodiazepines, Z-drugs and antidepressants does describe what hyperbolic tapering means in practice, but the recommendation enables flexibility in approach, and does not imply that dose reduction always has to follow a predefined trajectory, as that may not always be the most clinically appropriate approach for the person. An additional recommendation has been added to acknowledge use of published withdrawal schedules but notes that if used these should be applied flexibly. The BNF and NICE clinical knowledge summaries are updates in light of updates to NICE guidelines. NICE guidelines follow methodology set out in the NICE guidelines manual. If other guidance is incorporated it must meet the

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				recent guidance on stopping antidepressants issued by the Royal College of Psychiatrists, which has been endorsed by NICE: https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/management/benzodiazepine-z-drug-withdrawal/#withdrawing-a-benzodiazepine https://bnf.nice.org.uk/treatment-summary/hypnotics-and-anxiolytics.html Royal College of Psychiatrists Stopping Antidepressants https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants Yet this new guideline – which is dedicated to safe withdrawal and is all many doctors will read – provides none of this detail. We therefore urge NICE to include basic slow tapering information based on the publications above. **References re hyperbolic tapering:** Ashton, Heather. 2002. "Benzodiazepines: How They Work & How to Withdraw, The Ashton Manual."	same methodological criteria as set out in the methods manual, and the protocols relevant to the review question. All references provided have been checked but did not meet our review protocols, mostly due to not being appropriate study designs. The review protocols pre-specify the appropriate study designs that will be considered relevant to the type of review question. For the question on safe withdrawal randomised controlled trials and systematic reviews of randomised controlled trials were prioritised but if not available for a medicine class, comparative controlled trials. Non-comparative studies were excluded from this review as these would not provide sufficient quality evidence to inform recommendations on this topic. As this is an intervention review, qualitative studies were also not included. a result none of the suggested recommendations are relevant for inclusion within this review.

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				2002.http://www.benzo.org.uk/manual/bzcha01.htm. Framer, Adele. 2021. "What I Have Learnt from Helping Thousands of People Taper Off Psychotropic Medications." Therapeutic Advances in Psychopharmacology 11 (January): 204512532199127. Groot, Peter C., and Jim van Os. 2021. "Successful Use of Tapering Strips for Hyperbolic Reduction of Antidepressant Dose: A Cohort Study." Therapeutic Advances in Psychopharmacology 11 (August): 20451253211039330. Horowitz, Mark Abie, and David Taylor. 2019. "Tapering of SSRI Treatment to Mitigate Withdrawal Symptoms." The Lancet Psychiatry 6 (6): 538–46. Horowitz, Mark Abie, and David Taylor. 2021. "How to Reduce and Stop Psychiatric Medication." European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology 55 (October): 4–7.	

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				Sørensen, Anders, Henricus G. Ruhé, and Klaus Munkholm. 2021. "The Relationship between Dose and Serotonin Transporter Occupancy of ANTIDEPRESSANTS-a Systematic Review." Molecular Psychiatry, September.https://doi.org/10.1038/s41380-021-01285-w. Maudsley Prescribing Guidelines in Psychiatry, current edition	
APPG for Prescribed Drug Dependence	Guideline	007	013	'The risk of experiencing withdrawal symptoms' should be added as line 14 to match the information given for the other drugs above. This is already mentioned on P3 L4/5 "Antidepressants, although historically not classified as dependence- forming medicines, can cause withdrawal symptoms when they are stopped"	Thank you for your comment. The drug specific points have now been separated into standalone recommendations, and so a statement on the potential difficulties when stopping the medicines is included in the first recommendation of this section that covers all drug classes within the guideline scope.
APPG for Prescribed Drug Depe	Guideline	007	021	The management plan should include a 'discussion of all risks, including the risks of adverse effects, dependence and withdrawal'. The issue of adverse effects is acknowledged on P3, L12-13 and must be included here.	Thank you for your comment. The committee considered that other factors such side effects while important, were not specific to medicines associated with dependence and withdrawal included in this guideline but applied to all medicines. However, they do recommend that information about side effects is given to all people starting these medicines in recommendation 1.3.1.

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ndence					
APPG for Prescribed Drug Dependence	Guideline	012	005-007	The title of this section implies access to a medicine maybe cut off. PHE's PMR concluded that "inappropriately curtailing or limiting the use of medicines may increase harm, including the risk of suicide" (2019:118). Could the title be amended to 'Discussing the possible discontinuation of medicines associated with dependence and withdrawal symptoms"	Thank you for your comment. The first subheading in this section is 'Making shared decisions about withdrawing medicines' which sets out the need for this to be a shared decision between the person and the healthcare professional. The overall section title remains the same as this section contains recommendations focussing on more than just the discussions at the beginning of this process.
APPG for Prescribed Drug Dependence	Guideline	014	025-026	Add 'and can last for months or longer'. Evidence for protracted experiences of withdrawal is acknowledged in the PHE Prescribed Medicines Review report (e.g., p14, p118), and since the PHE evidence review was conducted new research has quantified this further: Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. January 2020. doi:10.1177/2045125320980573	Thank you for your comment. The committee agree it is important to acknowledge this in the recommendation and have added that they may vary in timing and that some may persist over a prolonged period. The reference you have kindly provided has been checked for inclusion in our evidence review on Withdrawal symptoms (Evidence review D). It does not meet our protocol and cannot be included in the evidence review it did not report themes emerging from qualitative data but performed a quantitative analysis, not allowing us to extract qualitative themes as required. The quantitative data presented does not meet the criteria to include as it is not an RCT.
APPG for	Guideline	014	010	Where will prescribers get this information from? Provide links to the NICE endorsed leaflet from	Thank you for your comment. This recommendation is worded as 'consider' as the committee agree it would only be

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Prescribed Drug Dependence				the Royal College of Psychiatrists 'Stopping Antidepressants' and the new Maudsley Prescribing Guidelines. https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants Maudsley Prescribing Guidelines in Psychiatry, current edition	appropriate for the healthcare professional to provide these if they are aware of high-quality sources that are available.
APPG for Prescribed Drug Dependence	Guideline	014	015	Include online groups and forums here	Thank you for your comment. The committee consider that online forums are adequately covered by the term 'sources of peer support'.
APPG for Prescribed Drug Dependence	Guideline	015	005	Information should be provided giving detailed information on this from existing NICE approved sources – links to BNF, Clinical Knowledge Summaries and RCPsych are: https://cks.nice.org.uk/topics/benzodiazepine-z-drug-withdrawal/management/benzodiazepine-z-drug-withdrawal/#withdrawing-a-benzodiazepine	Thank you for your comment. The BNF and clinical knowledge summaries are updated in light of NICE guidelines. Where the BNF already informs on a topic (for example on dose guidance) it is not necessary for that to be repeated in a guideline as healthcare professionals will also use the BNF. NICE guidelines follow methodology set out in the NICE guidelines manual. If other guidance is incorporated it must meet the same methodological criteria as set out in the methods manual, and the protocols relevant to the review question.

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				https://bnf.nice.org.uk/treatment-summary/hypnotics-and-anxiolytics.html Royal College of Psychiatrists Stopping Antidepressants https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants	
APPG for Prescribed Drug Dependence	Guideline	015	006	Mention consideration of how the dose advised can be created as it is reduced (including discussing the use of liquid alternatives where available – as mentioned P16/L11-12 of the Depression Guideline)	Thank you for your comment. This would vary according to the medicine, formulation and the reduction schedule. The committee therefore agreed that level of detail could not be provided within this guideline.
APPG for Prescribed Drug Dependence	Guideline	015	011	Patient groups report that gabapentinoids should be tapered at a proportionate, not fixed rate. Unclear what the evidence is for this and does not fit with current psychopharmacological theory, as per papers: Horowitz, Mark Abie, and David Taylor. 2021. "How to Reduce and Stop Psychiatric Medication." European Neuropsychopharmacology: The Journal of the	Thank you for your comment. This recommendation was formed by committee experience and knowledge of PHE and NHS reports on safe use of gabapentinoids, as well as the summary of product characteristics (SPC) guidance on tapering. These all recommend reducing by fixed amounts. In the committees experience most schedules are slower than the manufacturers recommendations in the SPC to minimise withdrawal and re-emergence of symptoms.

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				European College of Neuropsychopharmacology 55 (October): 4–7. Maudsley Prescribing Guidelines in Psychiatry, current edition	
APPG for Prescribed Drug Dependence	Guideline	015	014	Unless there is risk of severe harm, patients must have full control of the rate of their taper, not 'an element of control'. The wording in the new Depression Guideline could be used for consistency: 'ensure the speed and duration of withdrawal is led by and agreed with the person taking the prescribed medication, ensuring that any withdrawal symptoms have resolved before making the next dose reduction' 1.4.14 (P16/L13-16)	Thank you for your comment. While the committee agree that the dose reduction schedule and rate of reduction should be agreed with the person, which is stated in the recommendations, this bullet point was intended to give an additional element of control. The bullet point has been reworded to clarify what the intentions are.
APPG for Prescribed Drug Dependence	Guideline	015	028	It is essential that common withdrawal symptoms are listed and/or signposted so that doctors can distinguish these from other disorders or pathologies. The list now included in the NICE Depression Guideline (1.4.11) should be included (P15, L10-19).	The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these

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					symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary.
APPG for Prescribed Drug Dependence	Guideline	016	015	Note that depression is a common withdrawal symptom, and so following other NICE guidelines on depression may not be helpful until withdrawal is over (hence the importance of listing withdrawal symptoms)	Thank you for your comment. The cross reference to the depression guideline has been removed from this section.
APPG for Prescribed Drug	Guideline	016	020	Signposting peer support (both online and in person) could be usefully repeated here For all medicines, 'support from a clinician or therapist (for example, regular check-in phone calls, seeing them more frequently, providing	Thank you for your comment. Considering peer support is already included within the withdrawal section and so does not need to be repeated here.

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Dependence				advice about sleep hygiene)' should be added to be consistent with the Depression Guideline 1.4.13	
APPG for Prescribed Drug Dependence	Guideline	017	002	Can 'exceptional circumstances' be clarified? Unless there is a risk of severe harm, patients should be allowed to continue taking their medicines if they choose to do so, as withdrawal can be debilitating - it must not be imposed on someone unless absolutely necessary.	Thank you for your comment. On consideration of stakeholder comments received and review of this recommendation the term 'exceptional circumstances' has been removed from this recommendation.
APPG for Prescribed Drug Dependence	Guideline	018	General	There must be a research recommendation for hyperbolic tapering, especially rate of reduction and tapering duration for all classes of drugs in scope	Thank you for your comment. The recommendation for withdrawal of opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose. The committee therefore consider that this recommendation does describe what hyperbolic tapering means in practice, but the recommendation enables flexibility in approach, and does not imply that dose reduction always has to follow a predefined trajectory, as that may not always be the most clinically appropriate approach for the person. The committee agree that the description provided in the recommendations would be clearer to healthcare professionals. A research recommendation has not been included on taper rates as the committee agree this would not vary just by medicine, but also according to the needs and preferences of the individual, and the key would be an individualised flexible approach.

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APPG for Prescribed Drug Dependence	Guideline	018	General	There should be a research recommendation into the use of tapering strips to support safe withdrawal	Thank you for your comment. A research was included on practical aids and technologies to support withdrawal. The committee considered that tapering strips may be an example of a practical aid that could be considered here.
APPG for Prescribed Drug Dependence	Guideline	018	General	There should be a research recommendation into the differences between relapse and withdrawal, as withdrawal, in existing discontinuation trials, has not been controlled for satisfactorily. Nor are existing diagnostic tools sensitive enough to safeguard against such confounding.	Thank you for your comment. This was not a specific review question that was considered in the guideline and therefore a research recommendation has not been included in the guideline.
Association of Clinical Psychologists UK	Guideline	General	General	The ACP-UK commend the NICE Guidelines committee for addressing prescribed drug dependence and withdrawal for people with mental health problems. It is not clear to The ACP-UK why all psychotropic drugs are not included in this guideline when there is clear evidence that all psychotropic drugs have the capacity to be dependency forming and induce withdrawal effects. In particular the prescription of medicines aimed to help people experiencing psychosis should be included. The ACP-UK	Thank you for your comment. During the scoping for this guideline, it was agreed that medicines such as antipsychotics are outside the remit of this guideline, due to the requirement for specialist management. Guidance on their safe prescribing, monitoring and withdrawal is included within the NICE guideline for psychosis and schizophrenia in adults CG178. The context section has been reworded to clarify the definitions of dependence and addiction, as well as problems associated with dependence, which is used in the guideline

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				would like to see all psychotropic medicines included in these guidelines. We are concerned that there is not a common agreed understanding of the differences between dependence and addiction and therefore a scientifically accurate definition of dependence should be used within the guidelines so that the phenomena of dependence is accurately understood by both clinicians and patients.	recommendations. The recommendations also now clarify that dependence is an expected phenomenon of these medicines but that some people may experience problems associated with dependence.
Association of Clinical Psychologists UK	Guideline	General	General	We are concerned that the guidelines appear focused on withdrawal, rather than preventing dependence in the first place.	Thank you for your comment. The committee do not agree that this guideline focusses on withdrawal. Sections 1.1, 1.2 and 1.3 are all for when considering or starting a medicine associated with dependence or withdrawal symptoms and focus on issues pertaining to safe prescribing with a view to minimising risk of running into problems associated with dependence. Section 1.4 similarly focusses on review of these medicines to ensure continued safe prescribing. Section 1.5 does relate solely to withdrawal, but this is an important part of safe prescribing of these medicines and scope for this guideline.
Association of Clinical Psych	Guideline	General	General	We are concerned that there is no information within the guidelines on how different groups of people are prescribed medicines differently dependent on protected equality characteristics (Equality Act, 2010). It is well known that women are more likely to be prescribed 'anti-	Thank you for your comment. Although it is acknowledged that antidepressants may be overprescribed in women, it is also considered likely that depression is under diagnosed in men. The committee therefore agreed that the recommendations made in this guideline equally apply to women and men and have therefore not made separate

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ologists UK				depressants' and black men likely to be prescribed 'anti-psychotic' medication. In the past the Government did recognise the disparity between minoritised groups in mental health and introduced The Delivering Race Equality in Mental Health Care (2005) programme of work. At the very least the guidelines should include mandatory standards for training clinicians in equity, equality and prescribing as well as the requirement for services to audit and review prescribing practice on the basis of protected characteristics.	recommendations. An equalities impact assessment accompanies this guideline, this has been added to that form to acknowledge the consideration raised. Please note, antipsychotics are outside of scope for this guideline. Training in equity and equality applies to all remits of healthcare provided, and is not specific to this guideline. It is therefore outside of the remit of this guideline to recommend mandatory training standards.
Association of Clinical Psychologists UK	Guideline	General	General	NICE guidelines are the go to place for understanding what is best practice and what should be delivered to the population in terms of healthcare. Given the rise in prescribing antidepressants and other psychotropic drugs (Bogowicz et al., 2021) that cause dependence and withdrawal symptoms it is vital that the guidelines include standards around training Primary Care Practitioners including GP's who have as a group asked for more training in how to prescribe and stop medicines for mental health (MIND UK, 2018)	Thank you for your comment. The guideline provides recommendations for safe prescribing of the drug classes included within the scope; antidepressants, opioids, benzodiazepines, Z-drugs and gabapentinoids. The committee agrees that there are areas that may need support and investment, such as training costs, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are

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				Bogowicz, P., Curtis, H. J., Walker, A. J., Cowen, P., Geddes, J., & Goldacre, B. (2021). Trends and variation in antidepressant prescribing in English primary care: A retrospective longitudinal study. BJGP Open, 5(4), BJGPO.2021.0020. https://doi.org/10.3399/BJGPO.2021.0020 Mind UK. (2018). GP mental health training survey Summary. Mind.org.uk. https://www.mind.org.uk/media-a/4414/gp-mh-2018-survey-summary.pdf	prescribed these medicines. It is beyond the remit of this guideline to recommend training standards. The references you have provided have also been checked for inclusion in the guideline evidence reviews; however, they are not directly relevant to the review questions and therefore do not meet protocol criteria of the guideline evidence reviews.
Association of Clinical Psychologists UK	Guideline	010-011	016-021, 01-019	We are concerned that this recommendation (1.4) does not specify frequent regular medication reviews (1.4.1) or that the clinician closely monitor during the initiation phase or dosage changes of a drug of dependence (1.4.2). Rather than arranging review when the patient reports adverse effects as described in (1.4.3), the clinician should take the initiative to monitor closely. Without clear standards for practice patients will not receive a consistent, reliable, safe service.	Thank you for your comment. The committee's view is that the recommendations already include the points you raise. Recommendation 1.4.1 on the frequency of reviews does state that they need to be regular. This recommendation also includes a list of factors that indicate that more frequent

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					reviews will be required, including if the person is taking the medicine for the first time. Recommendation 1.4.2 states that the healthcare professional should consider increasing the frequency of reviews during dose adjustment. The committee agreed that it is important the review schedule is determined on the individual circumstances relevant to the person, and that required frequency would vary not only according to the medicine, but also for individuals. Therefore, they agreed it was not appropriate to recommend specific timeframes for frequency of review, but the need for regular review, with some situations requiring increased frequency is clearly stated in the recommendations. A recommendation was also included to highlight particular situations that might require more urgent review.
Association of Clinical Psychologists UK	Guideline	007-008	019-029, 001-004	We are concerned that this recommendation (1.3.3) does not advise clinicians to warn patients against taking drugs of dependence inconsistently.	Thank you for your comment. The committee have now added a statement to the recommendation about information to be given, highlighting that it should be explained to the person that missing doses may lead to symptoms of withdrawal.

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Association of Clinical Psychologists UK	Guideline	005	007-014	We are concerned that, as written, this recommendation (1.2.2) may incorrectly imply that the development of physiological dependence on a drug is related to a mental health diagnosis or addictive tendency rather than a natural physiological process that occurs when anyone takes a drug over a period of time. In addition this recommendation should include having a clear plan of action from the outset on how to address the mental health issue of concern that includes non-pharmacological approaches. There may well be circumstances where patients are prescribed psychotropic medicines for very long periods of time, but there should be a plan for how to stop prescribed medicines as appropriate from the outset.	Thank you for your comment. This recommendation was based on evidence from prognostic reviews, in evidence review E. Prognostic evidence from studies of opioids and benzodiazepines demonstrated an increased risk of developing problems associated with dependence in people diagnosed with mental health disorders including depression, anxiety, post-traumatic stress disorder, bipolar disorder, alcohol-use disorder or drug-misuse disorder. The committee agreed, based on their experience, that this also applies to Z drugs and gabapentinoids, but not to antidepressants, which are not dependence-forming medicines. The committee also noted that a comorbid mental health diagnosis can have a profound impact on people and increase their desire for medicines, and that people with a history of drug misuse may need higher drug doses to obtain the desired effect. This is stated in the rationale for the recommendation and in the discussion of the evidence in review E. Although it should be noted that management of specific conditions is outside of the scope of this guideline, recommendation 1.2.1 states that the healthcare professional should ensure that all relevant appropriate management options, including non-pharmacological treatment approaches and watchful waiting, have been discussed with and offered to the person before starting treatment with any of these medicines. A recommendation is also included in the

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					withdrawal section recommending that during withdrawal, continued management of the underlying condition is offered. The committee agree that it is important to have a plan on how to stop the medicine from the outset and to have discussed that with the person. Recommendation 1.3.1 included information about how it might be difficult to stop the medicine as something that should be included in information before starting a medicine. This has now been added to include providing information on how the withdrawal might be managed.
Association of Clinical Psychologists UK	Guideline	005	3 – 6	We welcome recommendation 1.2.1 in particular that non-pharmacological options should be offered before prescribing medicines that could induce dependence and future withdrawal symptoms. We would like this to be a mandatory standard that the Department of Health is obliged to fund.	Thank you for your comment. Guideline recommendations are not mandatory, but do provide best practice recommendations for the NHS.
Association of Clinical Psychologists UK	Guideline	007	002-012	We are concerned that this recommendation (1.3.1) incorrectly excludes antidepressants from drugs that may incur physiological dependence. There is substantial evidence that antidepressants do carry a risk of both dependence and withdrawal effects. Patients should be informed about the natural development of physiological dependence and	Thank you for your comment. The committee disagree that antidepressants are incorrectly excluded from dependence forming medicines. As stated in the context for this guideline, and in the scope, antidepressants are historically not classified as dependence-forming medicines, although they can nevertheless cause withdrawal symptoms when they are stopped. This is consistent with other reports on this topic, for

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				risk of withdrawal effects. Patients should be cautioned against accidental or deliberate inconsistent dosing, forgetting or skipping doses, or taking them off-schedule, as they may experience withdrawal symptoms that can be misinterpreted by clinician and patient alike as lack of psychiatric drug treatment effect (Fava et al., 2020; Howes et al., 2021) or a worsening psychiatric condition (Fava & Rafanelli, 2019), resulting in inappropriate treatment, such as increased prescriptions (Brath et al., 2018) or being prescribed multiple medications. Throughout the guidelines there is a need for guidance on how clinicians can distinguish withdrawal symptoms from a re-emergence of prior mental health problems. Line 8 is particularly problematic. It stops short of saying clearly that these medicines can be dependency inducing, and indeed are very likely to be dependency inducing. It is implied that a difficulty stopping might be difficult for the individual as if they have total control over this. Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances	example the Public Health England Prescribed Medicines Review published in 2019. The references you have provided have been checked for inclusion in the guideline evidence reviews. We note that most are provided for information in support of points made and therefore are descriptive articles/literature reviews rather than primary studies or systematic reviews of primary studies and are not relevant to include in any of the guideline reviews (e.g., Fava 2020, Howes 2021, Oliver 1999). Meyer et al. 2001, Haahr et al. 2014 and Solomon et al., 2005 is not relevant to the objectives of any of the guideline review questions. Brath 2018, Ho 2016, Kinrys 2019, Renoir 2013 are systematic reviews the aim and PICO of which did not match our review protocols. Studies included in the systematic reviews also did not match the study design prespecified in the guideline review protocols. Hengartner was checked for inclusion in the review on Withdrawal symptoms (Evidence review D). However, the study did not report themes emerging from qualitative data but performed a quantitative analysis, not enabling extraction of qualitative themes as required. The quantitative data presented does not meet the criteria to include within the intervention section of this question.

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				in Psychopharmacology. January 2020. Doi:10.1177/2045125320980573 Brath, H., Mehta, N., Savage, R. D., Gill, S. S., Wu, W., Bronskill, S. E., Zhu, L., Gurwitz, J. H., & Rochon, P. A. (2018). What Is Known About Preventing, Detecting, and Reversing Prescribing Cascades: A Scoping Review. Journal of the American Geriatrics Society, 66(11), 2079–2085. https://doi.org/10.1111/jgs.15543 Fava, G. A., & Rafanelli, C. (2019). Iatrogenic Factors in Psychopathology. Psychotherapy and Psychosomatics, 88(3), 129–140. https://doi.org/10.1159/000500151 Fava, G. A., Cosci, F., Guidi, J., & Rafanelli, C. (2020). The Deceptive Manifestations of Treatment Resistance in Depression: A New Look at the Problem. Psychotherapy and Psychosomatics, 1–9. https://doi.org/10.1159/000507227 Haahr, M. E. et al. (2014) 'Central 5-HT4receptor binding as biomarker of serotonergic tonus in humans: A [11C]SB207145 PET study', Molecular	

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				Psychiatry, 19(4), pp. 427–432. Doi: 10.1038/mp.2013.147. Hengartner MP, Schulthess L, Sorensen A, Framer A. Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum. Therapeutic Advances in Psychopharmacology. January 2020. Doi:10.1177/2045125320980573 Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029 Howes, O. D., Thase, M. E., & Pillinger, T. (2021). Treatment resistance in psychiatry: State of the art and new directions. Molecular Psychiatry. https://doi.org/10.1038/s41380-021-01200-3 Kinrys, G. et al. (2019) 'Tachyphylaxis in major depressive disorder: A review of the current	

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				state of research', Journal of Affective Disorders. Elsevier B.V., 245(October 2018), pp. 488–497. Doi: 10.1016/j.jad.2018.10.357. Meyer, J. et al. (2001) 'The Effect of Paroxetine on 5-HT2A Receptors in Depression: An [18F]Setoperone PET Imaging Study', American Journal of Psychiatry, (January), pp. 78–85. Oliver, James S., Graham D. Burrows, and Trevor R. Norman. 1999. Discontinuation Syndromes with Selective Serotonin Reuptake Inhibitors Are There Clinically Relevant Differences ? 12 (3): 171–77. Renoir, T. (2013). Selective Serotonin Reuptake Inhibitor Antidepressant Treatment Discontinuation Syndrome: A Review of the Clinical Evidence and the Possible Mechanisms Involved. Frontiers in Pharmacology, 4. https://doi.org/10.3389/fphar.2013.00045 Solomon, D. A. et al. (2005) 'Tachyphylaxis in unipolar major depressive disorder.', The Journal of clinical psychiatry. United States, 66(3), pp. 283–290. Doi: 10.4088/jcp.v66n0302.	

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Association of Clinical Psychologists UK	Guideline	007	014	We are unaware of the evidence for the assertion on line 14 (recommendation 1.3.1): *that the effect of the medicine may occur slowly and they might experience side effects before noticing any benefit* this may mislead both clinicians and patients that a medicine will definitely work, and give the impression that the patient just needs to persevere.	Thank you for your comment. This was informed by qualitative evidence identified in evidence review A. Evidence rated as high confidence, showed that people were unsure about the time taken for antidepressants to start having a therapeutic effect, and people are not aware that side effects can occur before the therapeutic effects. The review findings indicated that people did not think they were always given information about harms before starting treatment but if people are aware of this early on, this could facilitate coping with side effects. They also noted that in their experience people being prescribed gabapentinoids can experience a time lag between the initiation of treatment and any benefits. The committee agreed it is important to emphasise the time lag between the initiation of treatment and any anticipated benefits, and that side effects may occur before the benefits. It is important not to disregard the side effects and to emphasise that these side effects are likely to settle over time. It was agreed that the time lag can vary depending on the indication for which the medicine is prescribed. This is detailed briefly in the rationale for this recommendation and in more detail in the discussion of the evidence in evidence review A.

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Association of Clinical Psychologists UK	Guideline	008	017-022	Given that patients in secure settings are likely to be the most vulnerable, have the most restrictions placed upon them and the least amount of choice and control, we are extremely concerned that the guidelines recommend in 1.3.6 that a service setting dictates safe prescribing practice. This also relates to the issue that men and racially 155andomized155 people are more likely to be in those secure settings. As this recommendation is currently presented as a 'given' we recommend an urgent review of what is the prescribing practice in secure settings as the guidelines give the impression that there are different standards operating. We would recommend all settings have the same high standards of practice but that audits, reviews and training is even more pertinent in these settings.	Thank you for your comment. The committee agree that the same standards of practice and safe prescribing should apply in all settings. Recommendation 1.3.9 (formerly 1.3.6) addresses some specific situations, such as where dispensing is only possible once a day or people do not hold their own supplies of medicines. Examples such as these mean that some separate considerations may be required, but otherwise all recommendations do still apply.
Association of Clinical Psychologists UK	Guideline	008	013-016	We commend this Prescribing Strategies recommendation (1.3.5) that clinicians start with a low dose and include the patient in collaborative care. We are concerned that the follow-up process is not more concretely explained.	Thank you for your comment and support for this recommendation. The committee agree that a plan for follow up and review is important, and this is reflected in the recommendations. Recommendation 1.4.1 on the frequency of reviews does state that they need to be regular. This recommendation also includes a list of factors that indicate that frequent reviews will be required, including if the person is taking the medicine

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					for the first time. Recommendation 1.4.2 states that the healthcare professional should consider increasing the frequency of reviews during dose adjustment. The committee agree it is important the review schedule is determined on the individual circumstances relevant to the person, and that required frequency would vary not only according to the medicine, but also for individuals. Therefore, they agreed it was not appropriate to recommend specific timeframes for frequency of review, but the need for regular review, with some situations requiring increased frequency, is clearly stated in the recommendations.
Association of Clinical Psychologists UK	Guideline	008	005-006	We are concerned that this recommendation (1.3.4) does not emphasise close monitoring during the initiation phase or dosage changes of a drug of dependence or give a measurable standard for what close monitoring is.	Thank you for your comment. Recommendations for review are included in section 1.4. Recommendation 1.4.1 on the frequency of reviews does state that they need to be regular. This recommendation also includes a list of factors that indicate that frequent reviews will be required, including if the person is taking the medicine for the first time. Recommendation 1.4.2 states that the healthcare professional should consider increasing the frequency of reviews during dose adjustment. The committee agree it is important the review schedule is determined on the individual circumstances relevant to the person, and that required frequency would vary not only according to the medicine, but also for individuals. Therefore, they agreed it was not appropriate to recommend specific timeframes for frequency of review, but the need for regular

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					review, with some situations requiring increased frequency, is clearly stated in the recommendations.
Association of Clinical Psychologists UK	Guideline	008	010-011	We are concerned that this recommendation (1.3.4) suggests drug dosage increases are an expected outcome of psychotropic medication reviews. Although this is common practice, British Association for Psychopharmacology guidelines (Cleare et al., 2015) found it is supported only by custom, not by evidence when it comes to antidepressants specifically: A systematic review found no consistent evidence for increased efficacy after dose escalation in non-responders compared with continuing lower doses for SSRIs in seven RCTs, but in most studies the timing of dose increase was rather early (3–6 weeks) (Adli et al., 2005). Three large157andomizedd double-blind studies found that raising the dose of sertraline and fluoxetine has no benefit over staying on the original dose (Dornseif et al., 1989, Licht and Qvitzan, 2002; Schweizer et al., 2001). Indeed, the Licht and Qvitzan study reported that raising the dose of sertraline in non-responders at 6 weeks from 100 mg to 200 mg a day under157andomizedd double-blind conditions had a significantly	Thank you for your comment. This recommendation has been reworded to say, 'check whether the dose needs to be adjusted and, if so, how to do this safely.' So, it does not separate increase or decrease in dose. An additional statement has also been added to recommendation 1.3.8 in the prescribing strategies section to clarify that if a satisfactory response to a medicine is achieved but subsequently lost, this may be for a number of reasons including tolerance, and in that circumstance medicines should not be automatically escalated. The references you have provided have been checked for inclusion in our evidence reviews those provided for information relevant to points raised are not relevant to include due to being descriptive articles (Cleare 2008, Malhi 2019). The aim and PICO of systematic review by Ho did not match of the guideline review objectives as it focusses on efficacy. Studies included in the systematic review also did not match the review objectives.

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				poorer outcome than staying on the lower dose. As higher doses are associated with a greater risk of adverse events and discontinuation effects, raising the dose of these drugs may increase the risk without the benefit of better efficacy. There are major factors for non-response to drug treatment that cannot be remedied by increasing drug dosage. Ho et al., 2016 estimated about 50% of patients may not adhere to regular drug schedules, experiencing adverse effects, such as withdrawal symptoms, which may cause the patient to report non-response to the current drug dosage. Misdiagnosis is another contributor to reported non-response (Cleare, 2015; Malhi et al., 2019), as the patient may have received inappropriate treatment to begin with. Increase in dosage should not be automatic for non-response or any patient complaint. For the sake of patient safety, NICE guidance should state increase in drug dosage should be undertaken only when reasons for non-response, such as lack of a true psychiatric condition or non-adherence to a regular drug schedule, have been ruled out, and risk of increased adverse drug effects due to dosage increase is low.	

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				Cleare, A., Pariante, C., Young, A., Anderson, I., Christmas, D., Cowen, P., Dickens, C., Ferrier, I., Geddes, J., Gilbody, S., Haddad, P., Katona, C., Lewis, G., Malizia, A., McAllister-Williams, R., Ramchandani, P., Scott, J., Taylor, D., Uher, R., & the members of the Consensus Meeting. (2015). Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. Journal of Psychopharmacology, 29(5), 459–525. https://doi.org/10.1177/0269881115581093 Ho, S. C., Chong, H. Y., Chaiyakunapruk, N., Tangiisuran, B., & Jacob, S. A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. Journal of Affective Disorders, 193, 1–10. https://doi.org/10.1016/j.jad.2015.12.029 Malhi, G. S., Das, P., Mannie, Z., & Irwin, L. (2019). Treatment-resistant depression: Problematic illness or a problem in our approach? British Journal of Psychiatry, 214(1), 1–3. https://doi.org/10.1192/bjp.2018.246	

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Association of Clinical Psychologists UK	Guideline	011	021-029	We are concerned that this recommendation (1.4.5) does not remind the clinician to check for irregular dosing when patients report a change in their condition or a change in symptom pattern. Such irregularities may be the patient accidentally taking extra doses, skipping a dose, or taking drugs off-schedule.	Thank you for your comment. Although the committee agree this is an important factor in a review of prescribed medicines, they agreed that medicines adherence issues apply to all medicines and are not specific to those related to dependence and withdrawal symptoms that are included within these guidelines. Recommendation 1.4.4 cross refers to both the NICE Medicines adherence and Medicines optimisation guideline which cover this for all prescribed medicines.
Association of Clinical Psychologists UK	Guideline	014	025-026	This guidance (1.5.9) appears to be incomplete. Without specific withdrawal symptoms mentioned, GPs will not be informed about this and will not in turn be able to inform their patients. *withdrawal symptoms…can be physical or psychological* might be mis-interpreted to suggest that withdrawal symptoms might be physical or psychological *in origin,* whereas a more accurate phrasing would specify that 'withdrawal symptoms can be physical or psychological in expression'. All withdrawal symptoms are neurobiological in origin (Hyman and Nestler, 1996; Lerner and Klein, 2019). What causes the most confusion for doctors are psychological or emotional withdrawal symptoms, such anxiety, depressed mood, and	Thank you for your comment. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected

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				insomnia, because these are so easily mistaken for a return of the underlying condition – it would be important to specify these as neurobiogically induced in order to raise medical awareness of them. Otherwise, patients are likely to be misdiagnosed as having relapsed and restarted on unnecessary medication (Haddad & Anderson, 2007). Haddad, P. M., & Anderson, I. M. (2007). Recognising and managing antidepressant discontinuation symptoms. Advances in Psychiatric Treatment, 13(6), 447–457. https://doi.org/10.1192/apt.bp.105.001966 Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. doi: 10.1007/s00340-005-2128-3. Lerner, A., & Klein, M. (2019). Dependence, withdrawal and rebound of CNS drugs: An update and regulatory considerations for new drugs development. Brain Communications, 1(1). https://doi.org/10.1093/braincomms/fcz025	that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary. The references you have provided have also been checked for inclusion in the guideline evidence reviews but as they are descriptive reviews of literature they do not meet the guideline protocol inclusion criteria for study design.

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Association of Clinical Psychologists UK	Guideline	014	014	The guidance (1.5.8) contains this direction for clinicians: *explain how the withdrawal will be carried out* However, the guidelines do not include specific guidance on how to conduct a taper. It is essential to include this information.	Thank you for your comment. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that a healthcare professional can follow but enables flexibility in approach.
Association of Clinical Psychologists UK	Guideline	015	007-010	This advice (1.5.10) is incomplete and unclear. There is no specification as to what a 'slow, stepwise rate of reduction proportionate to the existing dose' entails. Without examples, clinicians will not be able to implement this advice.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the

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					recommendations do describe a schedule that a healthcare professional can follow but enables flexibility in approach.
Association of Clinical Psychologists UK	Guideline	016	015-018	We are concerned that by recommending psychological interventions for relapse prevention, this guidance (1.5.15) might suggest to clinicians that the psychological symptoms of withdrawal are relapse or that withdrawal itself is primarily psychosomatic. Whilst we welcome patients being offered psychological interventions and therapeutic support, which may help them cope with symptoms as they slowly recover from withdrawal, it should be made clear to the patient that the intervention is to help with the impact of the physiological effects. In addition patients should be supported by therapists specifically trained in working with prescribed drug dependence and withdrawal (Guy, et al., 2019). Guy, A., Davies, J., & Rizq, R. (2019). Guidance for Psychological Therapists: Enabling conversations with clients taking or withdrawing from prescribed psychiatric drugs. APPG for Prescribed Drug Dependence. https://prescribeddrug.info/guidance-for-psychological-therapists/	Thank you for your comment. The cross reference to the section on psychological interventions for relapse prevention has now been removed. The APPG report by Guy et al. was considered for inclusion in evidence review D (Withdrawal symptoms) but did not meet the review protocol study design inclusion criteria due to being grey literature.

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Association of Clinical Psychologists UK	Guideline	016	020	Whilst we understand that RCTs are lacking - as they are for all adverse treatment effects and that evidence is often not published from pharmaceutical research, the single most effective way to support withdrawal is to allow people to taper more gradually over a longer period, as shown in observational studies and our experience, as psychiatrists, clinicians and patient experts by experience, in tapering patients off drugs of dependence (Framer, 2021; Horowitz and Taylor, 2019). People experiencing psychotropic withdrawal should not be expected to control the symptoms of neurological upset or unbearable physiological withdrawal symptoms with mindfulness or reframing, or told that they have definitely reverted to their original psychiatric condition. They should be supported by therapists specifically trained in working with withdrawal (Guy, et al., 2020). Framer, A. (2021). What I have learnt from helping thousands of people to taper off antidepressants and other psychotropic medications. Therapeutic Advances in Psychopharmacology. https://doi.org/10.1177/2045125321991274	Thank you for your comment. When evidence is lacking, recommendations can be formed by committee knowledge and experience. The recommendations do already include stating that dose reduction should be done slowly, and may take several months or more. The references you have provided have been checked for inclusion in the guideline evidence reviews but do not meet the study design protocol inclusion criteria due to being descriptive articles/literature reviews (Framer 2021, Horowitz 2019), or grey literature (Guy 2020). As noted above, the committee's expertise informed recommendations and recommendations made are consistent with these suggestions.

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				Guy, A. et al. (2020) 'The "Patient Voice" - Patients who experience antidepressant withdrawal symptoms are often dismissed, or mis-diagnosed with relapse, or onset of a new medical condition', Therapeutic Advances in Psychopharmacology. SAGE Publications Ltd STM, 10, p. 204512532096718. doi: 10.1177/2045125320967183. Horowitz, M. A. and Taylor, D. (2019) 'Tapering of SSRI treatment to mitigate withdrawal symptoms', The Lancet Psychiatry. Elsevier Ltd, 6(6), pp. 538–546. doi: 10.1016/S2215-0366(19)30032-X.	
Association of Clinical Psychologists UK	Guideline	019	002-005	We are concerned about the research recommendation (4) focus on "Individual circumstances and the risk of dependence", which mistakenly looks for sociological or psychological triggers for the inevitable biological process leading to physiological dependence. This research recommendation is based on a misunderstanding of physiological dependence, a physiological process not related to social circumstances, distress, or co-morbid condition, but a predictable, homeostatic neurobiological	Thank you for your comment. This research recommendation has been reworded to look at the risk of problems associated with dependence, rather than the development of dependence. The references you have provided have also been checked for inclusion in the guideline evidence reviews however, we note they were included for information relevant to points made and are therefore descriptive articles/literature reviews, which do not meet the review protocols.

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				response to drugs that alter neurotransmitter levels for sustained periods (Hyman and Nestler, 1996; Lerner and Klein, 2019; O'Brien, 2011; O'Brien, 2018). The implication throughout this document that there are sociologically defined groups at higher risk of physiological dependence erroneously conflates physiological dependence with the psychological drivers associated with addiction. This also feeds into discriminatory beliefs towards marginalised and under-privileged groups. This misdirects clinicians' and researchers' attention away from the effect of long-term drug use on neural (and other) tissue and the important question of how to safely discontinue drugs of dependence. As written, this research aim will distract people and resources from the necessity to research optimal clinical use, prescription, and safe discontinuation of drugs of dependence instead. Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. doi: 10.1007/s00340-005-2128-3. Lerner, A. and Klein, M. (2019) 'Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new	

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				drugs development', Brain Communications, (2019). doi: 10.1093/braincomms/fcz025. O'Brien, C. (2011) 'Addiction and dependence in DSM-V', Addiction (Abingdon, England). 2010/10/06, 106(5), pp. 866–867. doi: 10.1111/j.1360-0443.2010.03144.x. O'Brien, C. P. (2018). Chapter 24: Drug Use Disorders and Addiction. In L. L. Brunton, R. Hilal-Dandan, & B. C. Knollmann (Eds.), Goodman & Gilman's The pharmacological basis of therapeutics. (13th ed.). McGraw-Hill Medical.	
Association of Clinical Psychologists UK	Guideline	023	030	Given the evidence already presented we are of the view that anti-depressants are dependency forming medicines.	Thank you for your comment. The committee do not agree that antidepressants are dependence forming medicines. As stated in the context for this guideline, and in the scope, antidepressants are historically not classified as dependence-forming medicines, although they can nevertheless cause withdrawal symptoms when they are stopped. This is consistent with other reports on this topic, for example the Public Health England Prescribed Medicines Review published in 2019.
Association of Clinic	Guideline	031	010	Given these guidelines support non-pharmacological interventions before prescribing, The ACP-UK would also recommend psychological and other non-	Thank you for your comment. Management of conditions for which these medicines are prescribed is outside of the scope for this guideline and therefore we are unable to make any

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al Psychologists UK				pharmacological interventions at the beginning of prescribing so that there the patient retains choice of treatment and may minimise the impact of dependency.	more recommendations than that already included to ensure these have been considered.
Bangor University	Guideline	General	General	With regard to drugs of concern, the guidance is not well targeted. It is both too broad, with much general good advice but little detail, and too narrow, excluding several drugs that are routinely cause withdrawal problems and are psychoactive such as beta-blockers and anticholinergics.	Thank you for your comment. The medicine classes to be included were agreed during the scoping process for this guideline. It was agreed that medicines prescribed for specific diagnoses in specialist settings were outside the remit of this guideline, due to the requirement for specialist management. This is also consistent with the Public Health England review on prescribed medicines. In many cases the committee agreed the evidence informed recommendations for general principles that applied to all medicine classes within the guideline scope. Where evidence suggested separate recommendations should be made for particular classes of drugs, separate recommendations have been made.
Bangor University	Guideline	General	General	There is a lack of conceptual clarity about the use of the term *dependence.* The attempt to address this in the Context preamble (p3, 16-25) is ambiguous, and this is reflected in ambiguities in the text. There has been debate over terminology for decades, but we suggest that with regard to prescription medication, it is helpful to make a distinction between *addiction behaviours* (avoiding a clear-cut distinction	Thank you for your comment. The context section has been reworded to clarify the definitions of dependence and addiction, as well as problems associated with dependence, which is used in the guideline recommendations. The recommendations also now clarify that dependence is an expected phenomenon of these medicines but that some people may experience problems associated with dependence.

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				between addiction and non-addiction, as recommended by Griffith Edwards when he described the Alcohol Dependence Syndrome in the 1970s) and *dependence* which refers to all difficulties in discontinuing medications other than loss of therapeutic benefit. *Dependence* is often a pharmacological effect that does not become apparent until withdrawal is attempted. *Addiction behaviours* are specific and problematic behaviours under conscious control but resisted, at least initially. In relation to opioids, *dependence* is inevitable during long term use, but is not necessarily very problematic. This is referred to in lines 22-25 on page 3 of the guidance, but there is no clarification of what the *problems of dependence* might be. What causes most difficulty with opioids is drug ineffectiveness and hyperalgesia. There are parallels in the case of benzodiazepines and gabapentinoids. *Dependence* only becomes a problem when the drug needs to be stopped or reduced, and these problems are easily overcome with low doses. Formulating problems and reasons for change as *dependence* (e.g. 1.4.5) can create confusion for patients and prescribers; the point is that some of these drugs can make the initial problem worse for some patients.	

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Bangor University	Guideline	General	General	Much of the guidance is counsel of perfection. It would have been difficult to deliver in primary care prior to the pandemic and assumes a degree of support which simply does not exist under current and foreseeable circumstances. Examples include: recommendations for initial assessment; delivery of information; agreement and carrying out of management plans; systematic medication reviews; co-ordination with secondary care; agreeing, carrying out and monitoring dose reductions. Recommendations relating to continuity of care in pursuing consistent management plans and patient reviews are not feasible given workload and chronic staffing problems experienced in primary care in all areas of the UK at present. The consequence is that GPs are likely to feel that they are being told what not to do, but lack the time resources and secondary care support to do what is more appropriate.	Thank you for your comment. The committee agree that there are areas that may need support and investment, such as training costs, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines. The committee are mindful of the pandemic. NHS services have been and continue to be adapting to implement interventions as appropriate following national guidance and restrictions relating to COVID-19, with social distancing where appropriate. The recommendations for review appointments note that these can be by phone, video or face to face. Implementation of the recommendations should take the current context into account.
BHIVA	Guideline	General	General	Sections 1.3.1 and 1.4.5 have helpful practical checklists for prescribers, which will aid discussion/ documentation. Overall, the document is quite wordy, so for ease of	Thank you for your comment. These are being produced to accompany the guideline on publication.

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				reference, it may be helpful to have these checklists in an executive summary or appendix.	
BHIVA	Guideline	007	017 – 018	Could there be some more specific information or examples / accredited patient leaflets / signposting to some national organisations?	Thank you for your comment. We are unable to endorse specific resources in the guideline as these will vary locally and provision can change.
BHIVA	Guideline	008	005	Is there expert opinion on the maximal time interval for reviews for all medicines in general, e.g., annual review at the very least?	Thank you for your comment. The committee discussed this but agreed that including a maximal time frame would risk that people are not seen any more frequently than this.
British Geriatrics Society	Guideline	General	General	The recommendations will be challenging to apply in practice because effective communication with the individual, outlying risks, benefits, agreeing and documenting a management plan and communicating effectively with colleagues in other sectors takes a lot of time and this will be difficult to implement within the current constraints within the health service. I*n the older patient age group in general and especially in those with conditions such as dementia active measures to ensure patient involvement in their prescribing and awareness of the risks and benefits of their medication is important. Knowledge of their medications, benefits and adverse effects should be passed on to the patients and/or next of kin and carers so there is an awareness of their medications and possible side effects. For example it is known that certain groups of medications*	Thank you for your comment. The guideline reflects the evidence for best practice. The committee agree that there are areas that may need support and investment, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines. Your comments will also be considered by NICE where relevant support activity is being planned.

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				including those used for analgesia eg antiepileptics are what is known as "FRIDS", Fall-risk increasing medications (see above) . Various modalities of analgesic medications can be FRIDs and so should be regularly reviewed in older patients to prevent falls and their consequences such as fracture and hospital admission. PMCID: PMC6435622 PMID: 30741371 **EuGMS Task and Finish group on Fall-Risk-Increasing Drugs (FRIDs): Position on Knowledge Dissemination, Management, and Future Research** L. J. Seppala,[#1] N. van der Velde,[#1] T. Masud,[2] H. Blain,[3] M. Petrovic,[4] T. J. van der Cammen,[5] K. Szczerbińska,[6] S. Hartikainen,[7] R. A. Kenny,[8,9,10] J. Ryg,[11,12] P. Eklund,[13] E. Topinková,[14,15] A. Mair,[16] L. Laflamme,[17] H. Thaler,[18] G. Bahat,[19] M. Gutiérrez-Valencia,[20] MA Caballero-Mora,[21] F. Landi,[22] M. H. Emmelot-Vonk,[23] the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs, A. Cherubini,[24] J. P. Baeyens,[25,26] A. Correa-Pérez,[27] A. Gudmundsson,[28,29] A. Marengoni,[30] D. O'Mahony,[31,32] N. Parekh,[33] F.	

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				E. Pisa,[34,35] C. Rajkumar,[36] M. Wehling,[37] G. Ziere,[38,39] and the EuGMS Special Interest Group on Pharmacology	
British Geriatrics Society	Guideline	004	011-012	The aim to foster collaborative trusting and supportive relationships is commendable but very difficult to achieve in clinical practice in both primary and secondary care due to the number of prescribers involved with some patients and pressures on services that make prescribing or review by one individual extremely difficult. Agree that clinical pharmacists in primary care could help with this. The patients taking regular analgesia may be vulnerable in terms of emotional and psychological health and a support system with an ongoing trusted health professional would help withdrawal processes.	Thank you for your comment. The committee agree that there are areas that may need support and investment to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines.
British Geriatrics Society	Guideline	005	019-023	These types of medications are commonly prescribed to people with dementia. Steps should be taken to facilitate their involvement in decision-making. It is particularly important to address the potential for withdrawal in Dementia patients as they are most likely to suffer adverse effects from the various medications that can be prescribed to relieve pain which can be of many modalities (eg opioids, adjuvant antiepileptics); furthermore these patients are	Thank you for your comment. The committee agree this is an important population to consider and equalities issue that should be reflected within the guideline recommendations and in the equalities impact assessment for the guideline. Additional recommendations have now been added for people with communication difficulties, such as people with learning disabilities or cognitive impairment. These include stating that necessary reasonable adjustments should be made to assist the individual and help them to understand the medicine options and their associated risks and benefits. This

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				also more likely to have remained on such medication without timely review and review should be built in to prescribing especially in older and physiologically more vulnerable patients.	has also now been included as a reason to consider more frequent reviews in recommendation 1.4.1.
British Geriatrics Society	Guideline	008	007	Regular reviews- agree that need to decide if the benefits of the medicine outweigh the harms but may need to do further monitoring to establish this e.g. lying and standing BP or U&Es to check for postural drop or SIADH in older people started on antidepressants (not specifically mentioned in the NICE depression guideline), and impact on cognitive function or falls (especially frail older people). There are also effects on cognition and mental functioning need to be actively looked for especially in older patients, in whom decline may occur gradually and it may be assumed to be part of the trajectory of their illness but still the effects of medications on cognitive function should be actively considered. Furthermore the risk of falls should be considered. Some analgesics are considered "FRIDS", Fall-risk increasing medications – see reference below:- -Drugs Aging. 2019; 36(4): 299–307. Published online 2019 Feb 11. doi: 10.1007/s40266-018-0622-7	Thank you for your comment. The committee agree that there are other factors that need to be considered as part of a medicines review. The recommendation in this guideline focusses on the elements that are particularly relevant to the risk of developing problems associated with dependence and withdrawal symptoms rather than condition specific factors. Medicines reviews are also covered in the NICE guideline for Medicines optimisation. The reference you have provided are beyond the remit of this guideline and therefore relevant to any of the review protocol inclusion criteria.

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				EuGMS Task and Finish group on Fall-Risk-Increasing Drugs (FRIDs): Position on Knowledge Dissemination, Management, and Future Research L. J. Seppala,[#1] N. van der Velde,[#1] T. Masud,[2] H. Blain,[3] M. Petrovic,[4] T. J. van der Cammen,[5] K. Szczerbińska,[6] S. Hartikainen,[7] R. A. Kenny,[8,9,10] J. Ryg,[11,12] P. Eklund,[13] E. Topinková,[14,15] A. Mair,[16] L. Laflamme,[17] H. Thaler,[18] G. Bahat,[19] M. Gutiérrez-Valencia,[20] MA Caballero-Mora,[21] F. Landi,[22] M. H. Emmelot-Vonk,[23] the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs, A. Cherubini,[24] J. P. Baeyens,[25,26] A. Correa-Pérez,[27] A. Gudmundsson,[28,29] A. Marengoni,[30] D. O'Mahony,[31,32] N. Parekh,[33] F. E. Pisa,[34,35] C. Rajkumar,[36] M. Wehling,[37] G. Ziere,[38,39] and the EuGMS Special Interest Group on Pharmacology. Drugs Aging. 2019; 36(4): 299–307. Published online 2019 Feb 11. doi: 10.1007/s40266-018-0622-7 -J Am Med Dir Assoc. 2018 Apr;19(4):371.e11-371.e17. doi: 10.1016/j.jamda.2017.12.098.	

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				Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics Lotta J Seppala [1], Anne M A T Wermelink [1], Max de Vries [1], Kimberley J Ploegmakers [1], Esther M M van de Glind [1], Joost G Daams [2], Nathalie van der Velde [3], EUGMS task and Finish group on fall-risk-increasing drugs -J Am Med Dir Assoc. 2018 Apr;19(4):372.e1-372.e8. doi: 10.1016/j.jamda.2017.12.099. Epub 2018 Mar 2.PMID: 29402646 Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink AMAT, van der Velde N; EUGMS Task and Finish Group on Fall-Risk-Increasing Drugs.	
British Geriatrics Society	Guideline	009	002	A local healthcare team can take steps to try and ensure that prescribing practice is standardised baring in mind that different prescribers will have different skill levels and levels of experience but it is unclear how they would ensure that prescribing practice is standardised between teams. This would	Thank you for your comment. On consideration of stakeholder comments, this recommendation has been removed.

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				probably need involvement from medicines optimisation teams in primary care.	
British Geriatrics Society	Guideline	024	014	Standard release opioid preparations are less frequently associated with problems with dependence than modified-release. It may not be appropriate to use standard-release opioids depending on the condition being treated e.g. for severe pain, you may not want the peaks and troughs associated with standard release opioids as this may cause more side effects and less efficacy. When reviewing patients on slow-release opioid preparations for chronic pain, switching to standard-release can cause problems as people may associate these with use for breakthrough pain and may overuse these preparations, exacerbating problems. The opioid approach also seems inconsistent with that suggested for benzodiazepines (i.e. switching to longer-acting medications to aid withdrawal) [page 30, line 6-13].	Thank you for your comment. This was informed by the evidence review of risk factors associated with dependence which the committee agreed was consistent with their clinical experience. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise. The committee do not agree that the approach described in your comment for chronic pain is always true. Pain intensity often varies, and people can look for opportunities to reduce their opioid dose accordingly: people on standard release regimens tend to use lower average opioid doses (and are therefore exposed to fewer harms) than those on fixed dose modified release regimens. We have also made clear in this section that decisions about best formulation depend on the person's circumstances and, comorbidities. The committee note that this consideration is specific to opioids, in that modified release formulations have been

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					shown to be increased risk of associated with dependence in some people, but there was no evidence on formulation in relation to risk of dependence for the other medicine classes included in the guideline. This is different to the pharmacokinetic consideration relating to switching from a benzodiazepine with a short half-life to one with a longer half-life which can facilitate withdrawal from this class of medicines.
British Orthopaedic Association	General	General	General	The BOA is concerned that, with the current lengthy waiting lists, more patients are being put on to opioids in order to manage their escalating levels of pain. Consideration should be given as whether it is appropriate to prescribe opioids for patients with chronic conditions. Several studies have shown that opioid use is escalating in this patient cohort from a baseline 5% to as high as 40% in the 12 months preceding surgery, as levels of pain increase. This is of significant concern. Some patients are also remaining on opioids for significant periods post discharge, even when the source of pain has been removed. The use of opioids post operatively does not return to the 'baseline' level not even after the rehabilitation period is over and the patient seemingly well after successful surgery.	Thank you for your comment. The efficacy of the drugs for different conditions is outside of the scope for this guideline. Recommendations for (or against) treatment are covered within the condition specific NICE guidelines, including the NICE guideline for Chronic pain. Relevant published NICE guidelines will be updated to include a cross-reference to the Safe prescribing guideline once it is published.

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				Several studies have also shown that patients on opioids before surgery have more peri-operative complications, including • Kidney injury • Surgical site infections • Respiratory failure • A longer length of stay It is essential that 'safe prescribing' is considered for these patients: there must be an active plan in place to reduce (withdraw) their use following successful surgery and relief of pain.	
Challenging Behaviour Foundation	Guideline	general	general	The CBF's medication briefing paper CBF medication briefing paper (challengingbehaviour.org.uk) demonstrates how individuals with learning disabilities are frequently prescribed medication for reasons other than the what the medication is intended for. Families shared the following reasons given for why their relative had been prescribed anti-psychotic medication: • Behaviour described as challenging	Thank you for your comment. The committee agree this is an important population and equalities issue that should be reflected within the guideline recommendations and in the equalities impact assessment for the guideline. Additional recommendations have now been added to highlight that people with communication difficulties, such as people with learning disabilities or cognitive impairment, can find it particularly difficult to describe their symptoms, which may lead to medicines being prescribed inappropriately or not at all. Recommendations include what additional steps the prescriber should consider in this situation.

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				e.g., '*It's a quick fix in the absence of a functional assessment*' • Anxiety e.g., '*where he lives makes him anxious- the behaviour of the people he lives with the staff.*' • Sleep problem e.g., '*He needs to go for a walk daily, for his mental health, behaviour and sleep but it doesn't happen because of staffing*'. • To prevent placement breakdown e.g., '*It was suggested that unless he was medicated the school could no longer provide for his needs*' • Lack of access to local, specialist services before a trigger point Over 90% of families in the CBF report ' (STOMP 2016: A family carer perspective (challengingbehaviour.org.uk)) said that challenging behaviour was one of the main reasons that medication was prescribed for their relative. However, less than half had a Positive Behaviour Support Plan and families reported that little attention was given to the reasons why their relative was displaying behaviour described as challenging.	The medicine classes to be included were agreed during the scoping process for this guideline. It was agreed that medicines such as antipsychotics are outside the remit of this guideline, due to the requirement for specialist management. Guidance on their safe prescribing, monitoring and withdrawal is included within the NICE guideline for psychosis and schizophrenia in adults CG178.

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				This shows that individuals with learning disabilities are discriminated against during the medication prescription process. The NICE guidelines should advise more stringent prescription practices for this group given the history of inappropriate, unnecessary, and ultimately harmful poor prescribing practice. The NICE guidelines could potentially encourage medical professionals to have STOMP/STAMP awareness training to educate them about this issue. Furthermore, medication should only be prescribed to individuals with a learning disability if they have a diagnosis which requires medication.	
Challenging Behaviour Foundation	Guideline	general	general	Communicating with adults who have a learning disability: Throughout the NICE draft guidance there is reference to inclusion of the individuals' views and making sure treatment is understood by the individual. We support the emphasis on the importance of including the individual in their treatment. For individuals with severe learning disabilities who have limited verbal	Thank you for your comment. The committee agree this is an important population and equalities issue that should be reflected within the guideline recommendations and in the equalities impact assessment for the guideline. Additional recommendations have been added to address this including highlighting the need to make necessary reasonable adjustments to assist the individual understand the medicine options and their associated risks and benefits, and to express their view.

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				communication, necessary reasonable adjustments should be made and alternative methods of communication such as Makaton signing or picture exchange communication systems might be required to help the individual understand medication options and gather their views. Family members often know the individual best and therefore must also be consulted where appropriate to ensure that the individual's preferences are understood and taken into account. Furthermore, we would like to emphasise that involvement of family should be on an opt-out rather than opt-in basis with medical professionals actively seeking family involvement and feedback during any reviews or decision-making on the individual's care/health.	Whilst the committee agree that family members may be best placed to help ensure the individual's preferences are taken into account, they are also mindful of ensuring this is done with the individual's agreement as appropriate. This has therefore not been recommended on an opt-out rather than opt-in basis.
Challenging Behaviour Foundation	Guideline	General	general	Regarding draft guideline 1.2.7 on not prescribing this medication if it is not in the person best interest it should be considered what this means for people with learning disabilities. Available data from NHS Digital and Public Health England and anecdotal evidence of current practice suggests individuals with learning disabilities are frequently prescribed medication that is not in their best interest but rather in the best interest of the care provider	Thank you for your comment. The committee agree this is an important population and equalities issue that should be reflected within the guideline recommendations and in the equalities impact assessment for the guideline. An additional recommendation (1.2.9) has been added to address this, noting that a full assessment should be undertaken considering unmet needs, with consideration of non-pharmacological options before medicines. The

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				who is struggling to effectively support their behaviour. Public Health England estimate that: "Every day about 30,000 to 35,000 adults with a learning disability are taking psychotropic medicines, when they do not have the health conditions the medicines are for. Children and young people are also prescribed them." (NHS England » Stopping over medication of people with a learning disability, autism or both (STOMP) This distinction must be made clear. Challenging behaviour is frequently displayed as communication of an unmet need. Prescription of medication does not always meet this need, and instead it often reduces an individual's ability to communicate their needs. In addition, there have been cases where being on these medications have significantly impacted the limited abilities that the induvial had. For example, family carers have told us that antipsychotic/anti-depressant medications significantly reduced their relatives communication abilities. In our STOMP work (STOMP 2016: A family carer perspective	recommendation also cross refers to the NICE Guideline on challenging behaviour and learning disabilities. Please note, as per our response to your comment above, antipsychotics are outside the scope of this guideline.

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				(challengingbehaviour.org.uk)) one family carer described the impact of psychotropic medications on their relative: *"Zombie, walking into walls, difficulty speaking."* (Family carer) pg 11 The risks associated with prescribing medication to individuals with learning disabilities should be clearly defined in the NICE guidance.	
Challenging Behaviour Foundation	Guideline	general	general	It should be considered that adults with a severe learning disability should have more regular medication reviews and more careful monitoring. A number of recent scandals, such as Cawston Park and St Andrews Healthcare (St Andrew's Healthcare - Womens Service (cqc.org.uk)), have shown that providers are often ineffective at safely managing medications and this could further put learning disability inpatients at greater risk. Care providers often fail to keep accurate and up to date records of inpatients which means that there may also be inconsistency or confusion within care teams about what the correct dosage is. For example, in the recent Cawston Park review there was clear evidence of poor recording and	Thank you for your comment. Additional care needs, for example people with learning disability or cognitive impairment, has been added as a factor to consider for increasing the frequency of reviews in recommendation 1.4.1.

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				overmedication which could have ultimately played a role in the deaths of 3 patients with learning disabilities SAR-Rpt-Joanna-JonBen_FINAL-PUBLICATION02-June2021.pdf (norfolksafeguardingadultsboard.info).	
Challenging Behaviour Foundation	Guideline	general	general	The guidance must emphasise the importance of supporting and informing the families of individuals with learning disabilities for whom medication is being considered or already prescribed. Family carers often know the individual best and can be the most important advocates for those with learning disabilities, therefore, it is important to include them in decision making processes. The CBF have produced resources for family carers with information and support if their relative have or may be prescribed psychotropic medications (Medication - Challenging Behaviour Foundation). Early intervention is essential to make sure support is in place to meet an individual's needs and and prevent them from reaching crisis point where they may become more likely to be given an inappropriate prescription. In our STOMP survey (STOMP 2016: A family carer	Thank you for your comment. The committee agree this is important to include. The guideline includes a recommendation to ask people if they would like to have support during appointments from a family member, carer, advocate or other person close to them. Advocate has been added to this recommendation following stakeholder comments received. Additional recommendations have also now been added to highlight the additional considerations that may be required to ensure that people with communication difficulties are able to participate in shared decision making, and also to highlight the risk of prescriptions being made inappropriately in this context if appropriate consideration isn't taken.

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				perspective (challengingbehaviour.org.uk)) family carers agreed that: "*If somebody has been prescribed medication because they have behaviour described as challenging and the cause of the behaviour is because they don't like the person they are living with, then withdrawing medication is not going to help. There is a real likelihood that there will then be a reliance on other restrictive interventions, such as physical restraint or seclusion. In two years' time, there may very likely to a Call to Action regarding physical restraint."* – pg 4	
Challenging Behaviour Foundation	Guideline	general	general	It is important that the views of patients, including individuals with learning disabilities, are considered when the medication is prescribed. The views of adults with learning disabilities should not be dismissed when they refuse medications, and they still have the right to be listened to when decisions about their medical treatment are made. If they are deemed to not have decisional capacity, then their family and/ or advocate should be consulted. However,	Thank you for your comment. Additional recommendations have also now been added to highlight the additional considerations that may be required to ensure that people with communication difficulties are able to participate in shared decision making including the need to consult with family members or carers, with consent. The new recommendations also highlight the risk of prescriptions being made inappropriately in this context if appropriate consideration isn't taken.

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				far too frequently the CBF have heard stories of people with learning disabilities being forcibly medicated in an inhumane manner that is likely to result in trauma. For example in our STOMP work (STOMP 2016: A family carer perspective (challengingbehaviour.org.uk)) one family carer described the inhumane treatment their son faced when he refused medication: "*He has refused so they inject him under restraints. Three people hold my son so the doctor can inject him*." Pg 10 This shows that harmful and traumatic physical restraint is being used to enforce potentially inappropriate administrations of medication without the individual's consent. Our STOMP survey (2016) found that: *"For 61%, prescribing took place without consideration of capacity and consent and in the absence of a best interests meeting. If relatives were living away from the family home, family carers were often only informed after the decision to medicate or guessed because of a change in their relative's presentation."* Pg 10	

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				And furthermore, that in some cases adults with learning disabilities were administered medication without their knowledge. One family carer described that medication had been "*Crushed and mixed up with maple syrup.*" These practices are inhumane and against best practice. Every effort should be made to help the individual understand the medication prescription and gain their consent especially when these medications can have such a profound and long-lasting impact.	
Challenging Behaviour Foundation	Guideline	010-011	013	Regarding guideline 1.4.1 we agree that regular reviews should be carried out. It should be noted that while offering virtual reviews is a good idea it may not be suitable for patients with a learning disability. Furthermore, we would advise that the guideline give a more specific timeline for what can be considered a 'regular review' for example, every 4-6 weeks. We also recommend that if someone has a learning disability they should be considered for more frequent reviews due to the high levels of risk previously explained in regard to the inappropriate or	Thank you for your comment. The committee agree that virtual reviews are not always appropriate for everyone, the recommendation does not specify how these should be held, but acknowledges that phone, video or face to face is an option. The committee considered that the necessary frequency of review would vary between people, depending on their personal circumstances as well as the drug they were

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				overmedication of this group. Furthermore, we would suggest that there are medication reviews of all adults with learning disabilities who are currently on psychotropic medications and don't have a mental health diagnosis and support given to these people to safely withdraw from these medications and find alternative, effective treatments. As medication is reduced, care needs to be taken to make sure that this does not result in an increase in another restrictive practice	withdrawing from and therefore a specific timeframe could not be recommended. People with additional care needs, for example people with learning disabilities or cognitive impairment have been added as an example that might require more frequent review.
Challenging Behaviour Foundation	Guideline	005	007-014	Regarding draft guideline 1.2.2 on the factors associated with increased likelihood of dependence having a learning disability should be considered a risk factor. Adults with learning disabilities are more likely to be inappropriately prescribed these medications. Furthermore, many adults with learning disabilities have limited or no verbal communication and may not be able to voice their own concerns around dependency. This puts them at increased risk of becoming dependent on these medications. Family members and others who know the individual well must be consulted when decisions are being made around prescribing	Thank you for your comment. The factors that are listed in 1.2.2 were informed by an evidence review of the literature (evidence review E). The committee acknowledge the points you raise, and have now included additional recommendations about the additional considerations required for people with communication difficulties or challenging behaviour to address these, rather than including these as a risk factor for developing problems associated with dependence.

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				medication. In addition, families known to the CBF have shared that service providers can request doctors/ prescribers to increase the dose of a particular medication given to adults with learning disabilities when incidents of challenging behaviour increase (without consideration of the reasons for the challenging behaviour or consultation with the individual or their family). This means adults with learning disabilities are at increased risk of high doses of inappropriate medication, making dependency more likely to occur.	
Challenging Behaviour Foundation	Guideline	005	001-006	Regarding draft guideline 1.2.1 about making sure that all relevant management options have been offered and discussed with the individual, families we support often tell us that in their experience this rarely happens for their adult relative with learning disabilities. Frequently antipsychotic and antidepressant medication is inappropriately given to adults with learning disabilities without a diagnosis of psychosis or depression, to reduce their challenging behaviour. the prescription of antipsychotic and antidepressant medication without a relevant diagnosis occurs far more frequently for adults	Thank you for your comment. The committee agree this is an important population to consider and equalities issue that should be reflected within the guideline recommendations and in the equalities impact assessment for the guideline. An additional recommendation (1.2.9) has been added to address this, noting that a full assessment should be undertaken considering unmet needs, with consideration of non-pharmacological options before medicines. The recommendation also cross refers to the NICE Guideline on challenging behaviour and learning disabilities.

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				with learning disabilities than adults in the general population (Prescribing - NHS Digital). Statistics from NHS Digital show that 11.6% of patients with a learning disability (without a diagnosis of depression) were given antidepressants compared to 4.4% of patients without a learning disability (without a diagnosis of depression). Furthermore, 15.2% of patients with a learning disability were treated with antipsychotics compared to 0.9% of patients without a learning disability. Similarly, patients with a learning disability were more frequently prescribed benzodiazepines compared to patients without a learning disability (7.2% compared to 2.1%). (Prescribing - NHS Digital) Therefore, appropriate prescribing should be seriously considered before medicating adults with learning disabilities. There should be a focus on understanding the reasons for challenging behaviour displayed by an individual before medication is considered. Furthermore, Positive Behavioural Support training has shown that non pharmaceutical treatment options can be far more effective at reducing challenging behaviour than medications Medication - Challenging Behaviour	

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				Foundation. This should be emphasised in the draft guidelines.	
Challenging Behaviour Foundation	Guideline	011	009-011	Regarding guideline 1.4.2 on increasing the frequency of reviews during dose adjustment. We agree on the importance of increasing reviews when doses are reducing but would emphasise that for people with learning disabilities, there should also be increased frequency of reviews when the dose is increasing.	Thank you for your comment. This recommendation was phrased as 'dose adjustment' to cover both increases or decreases in dose as you suggest. However, we have now removed the caveat 'especially during dose reduction' to strengthen that point. Additional care needs (for example people with learning disabilities) has also been added as one of the examples that might require more frequent reviews.
Change Grow Live	Guideline	General	General	The advice in the guideline is quite generalised. More practical advice on safe prescribing, specifics pertaining to dose reduction and management of withdrawal symptoms would be really helpful to clinicians. The guideline lacks these clinical details that are vital to ensuring that clinicians are able to implement the suggested guidance.	Thank you for your comment. The recommendations are based on the best available evidence. In many cases the committee agreed the evidence informed recommendations for general principles that applied to all medicine classes within the guideline scope. Where evidence suggested separate recommendations should be made for particular classes of drugs, separate recommendations have been made. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They made recommendations to guide the general

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					principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose and for gabapentinoids by a fixed amount each time. Similarly, the evidence for withdrawal symptoms is very limited in quantity and quality. The committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary.
Change	Guideline	General	General	Suggestion that it would be helpful to have shorter durations of prescribing supported as standardised pack sizes that make a shorter	Thank you for your comment. The committee discussed possible recommendations for prescription amounts and length however, there was no evidence identified to inform

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Grow Live				course/reduction apparent from the outset – and prescribers should be encouraged to not prescribe pack sizes of larger amounts (e.g. 56 or 100) which have been previously evidenced to increase risk of dependence. • Suggestion of shorter dispensing periods/amounts if high risk of dependence to reduce the risk of overindulging (and the associated escalation of doses that is often required), which is often successful for more impulsive individuals	specific recommendations on this, and the committee agreed this would vary according to medicine and condition. They agreed that prescription length should reflect the management plan (including plans for review), controlled drugs guidance and relevant legislation. Recommendation 1.3.5 has been amended to state that the duration of each the prescription that will be issued should be included in the management plan. The prescribing strategies recommendations refer back to this noting that prescribing should be consistent with the management plan. The committee agreed it was not possible to make recommendation on specific volumes or duration of prescriptions as this would vary between medicines, however, they do agree it is important to consider at each review. It is beyond the remit of NICE guidelines to make recommendations on the standardised sizes of medication packages.
Change Grow Live	Guideline	001	007	Certain drugs and categories of drugs that are also associated with dependence and / or withdrawal symptoms are not included in the scope of the guideline. Central Nervous system stimulants such as amphetamines and Central Nervous System depressants such as	During the scoping for this guideline, it was agreed that medicines requiring specialist management were outside the remit of this guideline. This includes amphetamines, barbiturates and antipsychotics.

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				barbiturates can also cause withdrawal symptoms. Barbiturates cause dependence with prolonged use and abrupt withdrawal should be avoided. Also, antipsychotics such as clozapine require careful withdrawal.	
Change Grow Live	Guideline	007	020-021	Can the following also be considered in the list of specifics to include in the management plan: • Any associated monitoring that should / will take place and when (specific patient parameters that should be monitored before / during / after treatment as opposed to general medical reviews) Guidance around missed doses (what to do in the event that the patient forgets to take a dose etc)	Thank you for your comment. The recommendation for the management plan does already include the plans for reviewing the medicine (including where and by whom this will be done) and the date of their next review. The later recommendations include detail on the content of the review (1.4.5). An additional bullet point has been included in the recommendation of information that should be given to the person before starting treatment, that missing doses may lead to symptoms of withdrawal. However, the committee considered that detail about missing doses and how to take the medicine applied to all medicines, not just those associated with dependence and withdrawal covered in this guideline and was also covered in the NICE guidelines on Medicines adherence and Medicines optimisation which are cross-referred to in the section for reviewing medicines.
Change Grow Live	Guideline	008	016	*'…determine the lowest effective dose in a reasonable time'*–- can more clarity be provided to clinicians on what constitutes a 'reasonable time'? Generalised guidance around timeframes would be really helpful.	Thank you for your comment. The committee agree this is not helpful in the recommendation and have removed 'in a reasonable time'. The committee consider that this would vary according to the individual and therefore a timeframe cannot be recommended.

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Change Grow Live	Guideline	010	016-017	*'Offer regular reviews (by phone, video or face to face) to people taking an opioid, benzodiazepine, gabapentinoid, Z-drug or antidepressant'* – can more clarity be provided to clinicians on what constitutes a 'regular review'? Generalised guidance around timeframes would be really helpful. For instance, for patients on opioid substitution therapy, the Orange Guidelines (page 111) state *'The frequency of patient review should reflect risk assessment and progress against agreed goals. Patients on opioid substitution treatment will need to be seen more frequently (at least fortnightly) initially and then, if stable, less frequently, such as once a month. Depending on local service arrangements and quality of support available, prescribers may feel their patient can be reviewed as little as every three months.'*	Thank you for your comment. The committee considered that the necessary frequency of review would vary between people, depending on their personal circumstances as well as the drug they were withdrawing from. They made a recommendation to state that regular intervals for reviewing the reduction schedule should be agreed, and also that frequency of reviews may need to be increased particularly during dose adjustment. The committee agreed that providing a minimum time period may risk people being seen no more frequently than this. A recommendation was also included to highlight particular situations that might require more urgent review. The committee noted that while opioid substitution therapy is used for illicit drug misuse and dependence (where the orange book applies), there is no evidence that this is an effective strategy for dependence on prescribed medicines, and no evidence was identified in the guideline reviews. Therefore the guideline recommendations differ from those in the Orange book.
Change Grow Live	Guideline	011	020-029	Can the following also be considered in the list of specifics to discuss in the content of reviews section: Detrimental effects of continuation of therapy – adverse effects etc (benefits from continuation are stated as discussion points but not disadvantages – these are also important to	Thank you for your comment. This bullet point has been reworded to include both the benefits and harms of continuing the medicine.

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				note when considering whether to continue with or to stop the medication.)	
Change Grow Live	Guideline	011	009-010	*'Consider increasing the frequency of reviews during dose adjustment, especially if the dose is being reduced.*' - Can more clarity be provided to clinicians around the extent to which the frequency of reviews should be increased? Generalised guidance around timeframes would be really helpful.	Thank you for your comment. The committee considered that the necessary frequency of review would vary between people, depending on their personal circumstances as well as the drug they were withdrawing from. The committee agreed that providing a minimum time period may risk people being seen no more frequently than this.
Change Grow Live	Guideline	014	018	More detail around withdrawal symptoms (specifics as opposed to generalised) in the guideline would be really beneficial to clinicians	Thank you for your comment. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected

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					that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary.
Change Grow Live	Guideline	015	007-010	More information on dose reduction and the proposed period of time over which reduction should take place (overall duration of tapering), would be really helpful to clinicians. For instance, regarding dose reduction (tapering) of benzodiazepine, the Maudsley Prescribing Guidelines state *'Most studies find that a gradual withdrawal over at least 10 weeks is most successful in achieving long-term abstinence, although many patients will require considerably longer.'* Generalised guidance around timeframes would be really helpful.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that a healthcare professional can follow but enables flexibility in approach, and does not imply that dose reduction always has to follow a

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					predefined trajectory, as that may not always be the most clinically appropriate approach for the person. An additional recommendation has been added to acknowledge use of published withdrawal schedules but notes that if used, these need to be applied flexibly.
Change Grow Live	Guideline	015	05	More details around how to reduce doses, tapering rates, time between dose reductions, and how to monitor and taper according to the patient's withdrawal symptoms, would be helpful to clinicians. For instance, the Maudsley prescribing Guidelines state the following, regarding tapering benzodiazepines: ***The process of tapering*** *Patients may be broadly risk stratified:* ■ *For low-risk patients (<6 months use, long half-life benzodiazepine, no experience of significant withdrawal symptoms in the past), a test reduction could be made of 25%.* ■ *For high-risk patients (>6 months use, short half-life benzodiazepine, past history of withdrawal symptoms) a test reduction of 5–10% could be recommended.* ■ *Reductions should be made according to a proportion (e.g. 10%) of the last dose. This means the reductions recommended will become smaller and smaller as the total dose is lowered.*	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that guides dose reduction but enables flexibility in approach. NICE guidelines follow methodology set out in the NICE guidelines manual. If other guidance is incorporated it must meet the same methodological criteria as set out in the methods manual, and the protocols relevant to the review question.

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				Most patients will be able to proceed between a rate of about 5–10% of their most recent dose per month. ■ *After reduction withdrawal symptoms should be monitored for 2–4 weeks, or until symptoms have resolved. Monitoring may take the form of simple measures of symptoms each day (e.g. out of 10) or using standardised benzodiazepine withdrawal scales.* ■ *Further reduction should be titrated to the tolerability of this experience. If symptoms are intolerable, an increase in dose, a period of stabilisation and more gradual reduction is needed. Mild, tolerable symptoms mean the reduction can continue to reduce at the same rate.*	
Change Grow Live	Guideline	015	018	*'Agree regular intervals for reviewing the reduction schedule'* - can more clarity be provided to clinicians on what constitutes a 'regular interval'? Generalised guidance around timeframes would be really helpful.	Thank you for your comment. The committee considered that the necessary frequency of review would vary between people, depending on their personal circumstances as well as the drug they were withdrawing from. They made a recommendation to state that regular intervals for reviewing the reduction schedule should be agreed, and also that frequency of reviews may need to be increased particularly during dose adjustment. The recommendation noting exceptional circumstances where abrupt withdrawal might be required also notes the need to consider more frequent reviews.

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Change Grow Live	Guideline	017	014	*'Consider scheduling more frequent reviews'* - Can more clarity be provided to clinicians around how frequently reviews should be scheduled? Generalised guidance around timeframes would be really helpful.	Thank you for your comment. The committee considered that the necessary frequency of review would vary between people, depending on their personal circumstances as well as the drug they were withdrawing from. They made a recommendation to state that regular intervals for reviewing the reduction schedule should be agreed, and also that frequency of reviews may need to be increased particularly during dose adjustment. The recommendation noting exceptional circumstances where abrupt withdrawal might be required also notes the need to consider more frequent reviews.
College of Mental Health Pharmacy	Guideline	General	General	Whilst it is positive to see a multidisciplinary committee, it is disappointing that given the focus is about medicines, only one pharmacist is included – especially when compared to 6 doctors for example. Furthermore, there is an absence of specialist pharmacist expertise specifically regarding mental health and addiction management While we welcome NICE's creation of guidelines regarding medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults, we believe that the draft guidance only touches the tip of what needs to be created. The guidelines have been long awaited by the sector	Thank you for your comment. The committee composition was agreed during scoping as the appropriate range of expertise to inform decision making for the guideline. The doctors all represent different expertise and specialisms that are involved in the prescribing and withdrawal management of medicines associated with dependence and withdrawal symptoms and so there is only 1 representative of each speciality, including the pharmacist. Candidates were appointed following interview, according to their suitability and expertise relevant to the guideline scope. The recommendations are based on the best available evidence. In many cases the committee agreed the evidence informed recommendations for general principles that applied to all medicine classes within the guideline scope. In most cases the committee agreed that specific recommendations

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				since the publication of the PHE evidence review in 2019 but the draft that has been published lacks detail and does not go deep enough in providing specific guidelines for different professions or medicines. In our following comments, we will highlight the guidelines that we believe need further detail or expansion. It may be useful to state the treatment setting e.g. for primary care? Noting there are further guidelines/restrictions in the secure environment for example Antidepressants: There were many comments received from CMHP members about antidepressants and the fact that the guidance very much sets antidepressants alongside medicines described as addictive or creating dependency; which could be considered "abusable". It was felt that this was not a helpful underlying message or narrative for this sort of guidance which will be developed into a patient version.	per medicine were not possible nor appropriate as an individualised flexible approach was most important. Where evidence suggested separate recommendations should be made for particular classes of drugs, separate recommendations have been made. These have been separated out from the general principles that apply to all medicines to make this clearer in the guideline. This guideline applies to all settings in which NHS care is provided or commissioned, as detailed in the scope. The committee agree that antidepressants are not dependence forming. This is stated in the context at the beginning of the guideline and reflected in the subheadings used throughout the guideline to clarify. Where recommendations are specific to problems associated with dependence, the medicines have been stated in the recommendation (not including antidepressants) to ensure this is clear. The committee also agree that there may be legitimate longer-term uses of some of these medicines, and for that reason agreed that long term use should not be considered a proxy for dependence. The guideline recommendations state that decisions to continue or withdraw from medicines should be made based on the balance of benefits and harms as well as other factors, including the persons preference and

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				Whilst antidepressants can cause withdrawal symptoms categorising them alongside benzos, gabapentinoids, and opiates is giving a different message. This has been commented on throughout the response. In addition with antidepressant we appreciate (and often agree) that antidepressants are not necessarily always prescribed appropriately, and so should be reviewed/withdrawn – there are a group of patients for whom antidepressants likely do provide a "prophylaxis" against further depression. Alcohol misuse management: There is no mention of alcohol management which may be a co-morbid management. We could not see any reference for a role for non-medical prescribers who have a role for continued management. There was no reference to NICE guidance for Anxiety Disorders which may be a co-morbid problem	therefore does not assume all should be withdrawn at a specific point in time. The guidelines should also be used alongside condition specific NICE guidelines including the NICE guideline for depression which at the time of responding to these comments, is being updated. Alcohol misuse management is outside the scope of this guideline. An amendment has been made to the recommendation of factors that may make withdrawal more difficult to acknowledge a history of problems associated with dependence as one such factor. This could include alcohol misuse. The guideline recommendations do not distinguish between medical and non-medical prescribers. The terms 'prescriber' or 'healthcare professional' have been used to encompass all who may be involved. We acknowledge there are a number of related NICE guidelines, these cannot all be cross-referred to within this guideline. This guideline will include a link on the 'finding more information section' to all relevant NICE guidance on medicines management, and all published guidelines covering use of medicines relevant to this guideline will include a cross-reference to these recommendations.

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College of Mental Health Pharmacy	Guideline	general	general	Given the definition for inclusion of prescribed medicines; ie that they can cause dependence and addiction, we think that nicotine products should also be included, as they certainly fit this criteria, are not without risks, (and costs) and prescribing needs longer term review.	Thank you for your comment. The medicine classes to be included were agreed at the scoping stage for this guideline. Nicotine products were not proposed as a group of medicines to include.
College of Mental Health Pharmacy	Guideline	general	general	As described above you have defined the included medicines, and highlighted the "considerable debate in relation to these definitions". However it should be added and emphasised that people never develop cravings for antidepressants. And therefore throughout the document the emphasis on antidepressants should be slightly different form that of the other medication.	Thank you for your comment. The committee agree that antidepressants are not dependence forming. This is stated in the context at the beginning of the guideline and reflected in the subheadings used throughout the guideline to clarify. Where recommendations are specific to problems associated with dependence, the medicines have been stated in the recommendation (not including antidepressants) to ensure this is clear.
College of Mental Health Pharmacy	Guideline	general	general	The document hasn't specified a scope of practice for application. Therefore we assume it applies to secondary care and specialist services.	Thank you for your comment. The detail on who the guideline is for is in the scope, and also at the start of guideline. This is defined as: • Healthcare professionals • Commissioners of NHS and local authority services • People using services, their families and carers, and the public. The broad terminology has been used to denote that this applies to all healthcare professionals in settings in which NHS care is provided or commissioned.

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College of Mental Health Pharmacy	Guideline	general	general	Throughout there is no reference to watching out for misuse or diversion this needs adding. Prescribers should ask the patient whether they are running out early, or supplementing the prescribed dose with top up doses, or with other medicines (licit or illicit – online supplies). Or whether they are giving/selling their supplies.	Thank you for your comment. Recommendation 1.4.5 about the content of reviews includes considering signs that the person is developing problems associated with dependence. Some examples are given, including running out of a medicine early or making frequent requests for dose increases. Illicit use of medicines is not within the scope of this guideline and therefore giving away or selling their medicines has not been included.
College of Mental Health Pharmacy	Guideline	general	general	Throughout there is no reference to volume /duration of supplies to be prescribed at a time. This needs adding to highlight the risk of accumulation and diversion.	Thank you for your comment. The committee discussed possible recommendations for prescription amounts and length however, there was no evidence identified to inform specific recommendations on this, and the committee agreed this would vary according to medicine and condition. They agreed that prescription length should reflect the management plan (including plans for review), controlled drugs guidance and relevant legislation. Recommendation 1.3.5 has been amended to state that the duration of each the prescription that will be issued should be included in the management plan. The prescribing strategies recommendations refer back to this noting that prescribing should be consistent with the management plan. The committee agreed it was not possible to make recommendation on specific volumes or duration of prescriptions as this would vary between medicines,

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					however, they do agree it is important to consider at each review.
College of Mental Health Pharmacy	Guideline	General	General	There is currently no information in the guidelines regarding out-of-hours support or access to emergency supplies; we would recommend adding this in as many people may require this, especially people experiencing isolation or living in rural areas.	Thank you for your comment. Consideration of models of service provision was outside of the scope of this guideline and therefore recommendations cannot be made on out of hours support.
College of Mental Health Pharmacy	Guideline	General	General	We welcome the recognition that intersecting dependencies and health issues must be included in any consideration regarding withdrawal, and encourage you to highlight this further in the guidance.	Thank you for your comment. History of problems associated with dependence has now also been added to the recommendation of factors to consider when considering withdrawal. While the committee agree that a holistic individualised approach is important throughout, health issues have not been added here as not all comorbid health conditions would lead to an increased risk of problems with withdrawal.
College of Mental Health Pharmacy	Guideline	General	General	Take home naloxone provision must be considered in the context of opioids.	Thank you for your comment. The committee acknowledged that take home naloxone is used in people with known current or history or substance misuse, however, it was noted that there is no evidence that this is an effective strategy for dependence on prescribed medicines, and no evidence was identified in the guideline reviews. The committee discussed that although it is a strategy that is beginning to be used in the US, there is much more cross over in the US setting of people with prescription drug dependence and substance

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					misuse problems. Therefore, this is likely to be a context-dependent strategy that is less likely to be relevant in the UK setting. This discussion is detailed in the discussion of the evidence in evidence review B.
College of Mental Health Pharmacy	Guideline	General	General	Please add more information about management of relapse including fast track into services, the risk of accidental overdose, role of harm reduction and naltrexone in the case of opioid maintenance of abstinence prescribing.	Thank you for your comment. Management of relapse was not within the scope of this guideline. Some condition-specific NICE guidelines do, however, include recommendations on this topic. The committee acknowledge that naltrexone is used for relapse in formerly illicit opioid dependent people or formerly alcohol dependent people, however, there is no evidence that this is an effective strategy for dependence on prescribed medicines, and no evidence was identified in the guideline reviews.
College of Mental Health Pharmacy	Guideline	009-010	general	In this section on "Working with other HCPs" please add: - that primary care prescribers must ensure that the SCR reflects ALL medicines that the patient is prescribed, from all prescribing teams, including specialists. Not just medicines prescribed from that services. This is key to medicines reconciliation and safe prescribing practices. - that when communicating about medicines, prescribers should list ALL medicines prescribed, ie not just those by their own service. Including doses and frequencies.	Thank you for your comment. Whilst the committee agree that it is important that the healthcare professional is aware of all medicines the person is taking, the remit of this guideline is medicines associated with dependence and withdrawal and therefore, the recommendation for the management plan focusses on these medicines. An additional recommendation has been included to state that when transferring care, ensure all relevant healthcare professionals have access to management plan. This section of the guideline does focus on prescribers (which includes pharmacists) and the person considering and/or taking the medicine, because this is about the decisions when considering or starting one of these

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				The focus of this section is very much on prescribers and there needs to be further consideration of other healthcare professionals who are involved in withdrawal, such as pharmacists and clinicians who are working in recovery support settings. There is currently no clear widely-adopted process for pharmacists to handle cases of people who are undergoing withdrawal management, and there needs to be. The guidelines need to be informed by a holistic approach to ensure that everyone who is interacting with the person is taking a cohesive approach to their case.	medicines and appropriate prescribing strategies. The sections that follow are about review and withdrawal of these medicines and do not focus only on the prescriber.
College of Mental Health Pharmacy	Guideline	012 - 013	General	Please add a new point to say that when considering withdrawing a medicine, prescribers should assess the patient holistically, considering whether they are stable psychologically and in mental state. There may be particular times when a patient us under social stressors or psychologically fragile, or about to go away for an extended period, and therefore that would not be an appropriate time to consider the withdrawal of a long term medicine, as it would be more likely to be unsuccessful.	Thank you for your comment. The committee do agree this is important to consider, however, this is already stated within the recommendations by discussing 'factors that might influence the timing of the start of the dose reduction, such as the person's circumstances and available support'. A statement has now been added to clarify that the timing of starting should also be discussed.

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				The timing of starting the withdrawal should be discussed with the patient.	
College of Mental Health Pharmacy	Guideline	003	016-025	Isn't this the "scope" of the document, rather than "context"	Thank you for your comment. The scope for the guideline is detailed in a separate document, available on the NICE website. This section relates to the need for the guideline with respect to the current context.
College of Mental Health Pharmacy	Guideline	003	Line 16-25	Perhaps consider reference to ICD to strengthen the position taken/points made.	Thank you for your comment. However, NICE do not routinely include references in the context section of guidelines. A hyperlink to the ICD-11 has not been added because the definitions within the ICD are split up according to opioid dependence, sedative hypnotic, anxiolytic dependence etc. rather than providing a single definition that would be a quick reference for readers of the guideline.
College of Mental Health Pharmacy	Guideline	003	011-013	Please emphasise the risk benefit need – notably for antidepressants in reducing suicide risk. It is important to avoid adding to stigma about the role of medicines for mental health wherever possible.	Thank you for your comment. The context section is intended to briefly set out the background and need for the guideline and therefore does not cover all issues related to the use of these medicines.

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College of Mental Health Pharmacy	Guideline	003	Line 29	medicines optimisation' appears superfluous in this context. Suggest remove "as part of medicines optimisation".	Thank you for your comment, this has been removed as suggested.
College of Mental Health Pharmacy	Guideline	004	Line 1-2	Please emphasise the impact of stigma here.	Thank you for your comment. This has been added.
College of Mental Health Pharmacy	Guideline	005	general	This section reads as only applicable to newly started medicines in out-patient settings and where a patient has capacity regarding their medicine decisions. If this is intended then please specify this context. This section is not realistic nor appropriate for most inpatient care settings where the balance of risks and benefits may be much more acute, and a shorter term perspective is needed; or in palliative care settings where the much longer term issues are not relevant.	Thank you for your comment. This section does not only apply to newly started medicines. The first recommendation (as well as others) starts 'Before starting or *continuing* treatment…' A recommendation is included relating to the first appointment (now reworded to 'the first appointment prescribing is discussed') however, the committee noted this

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				Nor relevant for patients who do not have capacity to make decisions about their medicines.	is important to include as well as some separate considerations do apply in that scenario. The recommendations also do not only apply in an outpatient setting, although it is of note that use of opioids for acute pain is excluded from this guideline. The committee acknowledge there may be some different considerations in an inpatient setting, but the general principles of safe prescribing of these medicines still apply. It is also important to note that use of opioids at the end of life is also excluded from this guideline. A recommendation is included in the section above (recommendation 1.1.2) to ask people whether they would like to have support during appointments from a family member, carer, advocate or other person close to them. This would be of particular relevance if the person does not have capacity to make decisions about their medicines. Recommendation 1.2.3 cross references the NICE guideline on shared decision making to support people when making decisions. A cross reference to the NICE guideline on decision making and mental capacity has now also been added to this recommendation as well.
College of Mental Healt	Guideline	005	general	If prescribing decisions are made for patients who lack capacity to participate, or who refuse to participate in medicine discussions, please add guidance to the prescribers about making these decisions and recording them.	Thank you for your comment. Recommendation 1.1.2 states that people should be asked whether they would like to have support during appointments from a family member, carer, advocate or other person close to them. This would be of particular relevance if the person does not have capacity to

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h Pharmacy					make decisions about their medicines. Recommendation 1.2.3 cross references the NICE guideline on shared decision making to support people when making decisions. A cross reference to the NICE guideline on decision making and mental capacity has now also been added to this recommendation as well.
College of Mental Health Pharmacy	Guideline	005	Section 1.2.3	Please rephrase the two suggested steps for clarity, e.g.: "Steps include - starting the medicine at a low dose and - when prescribing opioids avoid starting regular modified-release formulations, either on their own or together with a standard-release (immediate-release) formulations". And add the rationale for explanation.	Thank you for your comment. This was informed by the evidence review of risk factors associated with dependence which the committee agreed was consistent with their clinical experience. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise. Recommendations to perform benefit-harm assessment and to make a shared decision with the person still apply.
College of Mental Health	Guideline	006	Line 20	Please change "give" to "offer"	Thank you for your comment. The committee agreed it is important for everyone to have had this information given to them. This is not considered to override patient choice, as they can determine what to do that information. It's also important to consider that the person may not wish to read the information at the time of the appointment, but may wish to refer to it at a later date.

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College of Mental Health Pharmacy	Guideline	007	Line 17-18	We recommend deleting this weak recommendation, it may be more risky than helpful for many patients.	Thank you for your comment. There was some evidence reviewed that demonstrated that some people find peer support networks helpful. This recommendation has therefore been included to consider this as an option.
College of Mental Health Pharmacy	Guideline	007	General 1.3.1	Add an additional point about emphasising the anticipated benefits – again especially important for antidepressants. Also to add about the importance of continued psychosocial interventions alongside.	Thank you for your comment. This recommendation has been reworded to state 'any *beneficial* effect…'. Although the committee agree that non-pharmacological treatment should always be considered, ongoing management of specific conditions is outside the scope of this guideline.
College of Mental Health Pharmacy	Guideline	007	Line 8	Suggest rephrase, to instead emphasise practical steps to be taken to manage discontinuation of the medication in a way that minimises adverse effects – this is especially important so as not to discourage the use of antidepressants where they are clinically indicated.	Thank you for your comment. The committee consider that adverse effects of medicines cannot necessarily be avoided however, the recommendations for safe withdrawal of medicines are intended to minimise problems when withdrawing from these medicines. Recommendations on withdrawal of these medicines are in section 1.5. A cross reference to this section has been added to recommendation 1.3.1.

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College of Mental Health Pharmacy	Guideline	007	Line 17	We strongly recommend referencing free and confidential support services provided by the third sector.	Thank you for your comment. We are unable to endorse specific resources in the guideline as these will vary locally and provision can change.
College of Mental Health Pharmacy	Guideline	007	020	Section 1.3 – Prescribing strategies The points made are good, but would like to see something more specific in terms of advice on time-limited or "course" prescribing of benzos/z-drugs. Similar to principles of antibiotic prescribing i.e. indication, dose, duration, review. Please add guidance for how to proceed when you cannot "agree a management plan with the person" at the outset. It would be helpful to recommend that services build and develop systems and processes to support these management plans in order to deliver this. Eg templates within primary care prescribing systems. Under the bullet points please add: - "Treatment goals".	Thank you for your comment. The committee discussed including detail about the prescription length, however, they agreed that the appropriate length of each prescription would vary according to medicine and the condition being treated, and therefore it would not be helpful to provide a recommendation specifying within this guideline. However, they did agree it was important to include this detail within the management plan that was agreed and given to the person when being prescribed a medicine. Recommendation 1.2.7 is included to address situations where a shared decision cannot be reached. The guideline evidence reviews did not inform recommendations on practice policy templates or similar. However, the committee did make a research recommendation of relevance about the most effective

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				- the notable risks of the medicine, e.g. with interactions, with alcohol and other medicines/substances. - the common and high risk side effects. Add about psychosocial interventions/signposting as needed Suggest amend the last two bullet points into one: to review if the dose requires changing and how to do this suited to the needs of the individual. Again, strongly recommend emphasising the importance of checking about psychosocial interventions.	service models in supporting withdrawal from medicines associated with dependence and withdrawal symptoms. Treatment goals is already included as an item in the management plan as 'the intended outcome of treatment'. The committee considered that other factors such as medicine interactions and information about side effects while important, were not specific to medicines associated with dependence and withdrawal included in this guideline but applied to all medicines. However, they do recommend that information about side effects is given to all people starting these medicines in recommendation 1.3.1. The final 2 bullet points in recommendation 1.3.6 (which we think your final comment is referring to) have been combined and reworded to focus on dose adjustment. Recommendation 1.3.2 states that the healthcare professional should consider supplementing verbal and written information with details of peer support networks or online forums suitable for the person. Further support relevant to specific conditions is outside the scope for this guideline.
College of Mental Healt	Guideline	007	line 29	Delete this bullet point as it is too non-specific to be achievable: "r*isks of taking more than the prescribed dose"*	Thank you for your comment. The committee think this is important information to include when prescribing medicines associated with dependence and withdrawal. They do not agree it is not achievable to address this in discussions with the person and the management plan.

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College of Mental Health Pharmacy	Guideline	008	017	Please reword for clarity. We are not clear what this is attempting to say.	Thank you for your comment. Unfortunately, we are not sure which part of the recommendation this comment refers to, although we think this refers to recommendation 1.3.9 which addresses some specific situations, such as where dispensing is only possible once a day or people do not hold their own supplies of medicines.
College of Mental Health Pharmacy	Guideline	008	021	Suggest rephrase not just about other people living there but 'vulnerable others' e.g. visitors, including young people and also safe storage when transporting/outside of the home – as this is where notable learning from deaths have occurred.	Thank you for your comment. Although the committee note that vulnerable others may be of merit to consider in the recommendation, they consider that it is not just the vulnerable and have not added this. A separate consideration has been added to the recommendation of what information should be given to the person when starting treatment (1.3.1) to include information on safe storage of the medicine.
College of Mental Health Pharmacy	Guideline	008	025	Rephrase: "• should comply with best practice in controlled drugs prescribing and • must comply with relevant legislation" suggest: • must comply with all relevant prescribing legislation	Thank you for your comment. Advice on safe storage of controlled drugs is included within the NICE guideline for controlled drugs, which this recommendation cross-references to. A separate consideration has also been added to the recommendation of what information should be given to the person when starting treatment (1.3.1) to include information on safe storage of the medicine.

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				• prescriptions for all schedules of controlled drugs should comply with best practice in controlled drugs prescribing	
College of Mental Health Pharmacy	Guideline	009	004	After "*take the same level of care you would take if you were the original prescriber*" please add that this includes proactively reviewing and amending the prescription including doses. And under the last bullet point add that the primary care prescriber needs to know *how* to reduce the dose.	Thank you for your comment. The committee agree that the points you raise are true, however, all other recommendations in the guideline still apply to the healthcare professional in this context, and therefore these considerations have not been added to this recommendation as they are covered elsewhere.
College of Mental Health Pharmacy	Guideline	009	023	After "t*he primary care prescriber, who will review the need to continue the medicine*" please add that this includes amending doses Please widen to pan-interface settings medicines reconciliation issues not just between secondary and primary care e.g. specialist drug and alcohol treatment services, out of hours provision and prisons (especially prison releases/out of hour requests). Emphasise about the need for shared clinical management systems and timeliness of sharing of information	Thank you for your comment. The committee agree that the points you raise are true, however, all other recommendations in the guideline still apply to the healthcare professional in the contexts that you describe, and therefore these considerations have not been added to this recommendation.
College of Mental	Guideline	010	016	Please separate out the guidance for antidepressants. This doesn't read well for antidepressants, where at the start of therapy we should be focusing on treatment goals and	Thank you for your comment. There is a separate statement directly below this recommendation to also cross-refer to the NICE guidelines on depression in adults and depression in adults with a chronic physical health problem for more

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Health Pharmacy				the efficacy against symptoms, optimising doses (increasing) in order to fully treat symptoms. Moreover there is already guidance in the current Depression guidelines about the time intervals for reviewing treatment (especially in younger people). Please strengthen by adding specific reference to an individualised risk management plan/safeguarding. Also signpost to guidance where it exists for specific meds e.g. for z-drugs and the Orange guide.	information on antidepressants. Where statements have been made for different medicines in the guideline rather than general principles, these have now been separated out in the recommendations. Recommendation 1.4.4 also includes a cross-reference to section on medication review in the NICE guideline on medicines optimisation where recommendations are made that apply for all medicines. Hyperlinks to all condition specific guidelines are not included within this guideline document, however, they will be available on the NICE website. Resources produced by other organisations are not linked to or referenced in this document unless they informed evidence reviews, or evidence demonstrated they should be recommended.
College of Mental Health Pharmacy	Guideline	011	021	Please add treatment goals	Thank you for your comment. The management plan includes the intended outcome of treatment. It is noted that this should be updated at each review, and so this does not need to be restated in the recommendation as it would be part of the discussion about the benefits and harms the person is experiencing from the medicine.
College of Mental	Guideline	012	008	"Discuss withdrawing an opioid, benzodiazepine, gabapentinoid, Z-drug or antidepressant with the person if:	Thank you for your comment. Further recommendations in this section do go on to recommend that the risks of abrupt discontinuation should be explained to the person and what

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Health Pharmacy				• it is no longer benefiting the person • problems with dependency have developed • the condition for which the medicine was prescribed has resolved • the harms of the medicine outweigh the benefits • the person wants to stop taking the medicine." This section needs to be more explicit about the severe risks of withdrawing from some medications if not done properly, for example the guidelines should make clear that sudden cessation of benzodiazepines in dependency can be fatal if inappropriately managed and therefore the setting in which this should be done ie acute care. Also the role of e.g. symptomatic relief in the case of opioid withdrawal. We know this is important given inappropriate management also perpetuates use despite the ongoing harms in the case of dependency. Please could rephrase this section around "difficult conversations", acknowledging that these may be emotive issues.	to expect when withdrawing from these medicines, including how difficult it can be. Recommendations are included for CBT as symptomatic review when withdrawing from benzodiazepines informed by evidence reviewed in this guideline, and a further recommendation is included to consider treating the physical symptoms of withdrawal (for example, abdominal cramps and diarrhoea during withdrawal of an opioid). Recommendation 1.5.5 has been reworded slightly. The committee agree that there may be some prescribing decisions that weren't in the person's best interest. They acknowledge that it may not be possible to tell however, and have reworded the recommendation to add '*if sufficient appropriate clinical detail is available*, discuss the possibility that past prescribing was done in the person's best interests using the knowledge available at the time'.

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				Some past prescribing may have been done with good intention and based on good evidence, but some may not. If we are to acknowledge one practice, then we need to acknowledge the other possibility. Or neither.	
College of Mental Health Pharmacy	Guideline	12	008	In the bullet points please add: misuse, diversion and erratic adherence	Thank you for your comment. The committee believe issues such as these may be considered within 'if problems with dependency have developed'. However, illicit use is not within the scope of this guideline and so specific reference to misuse and diversion of prescription medicine is not included in the recommendations. They also note that erratic adherence may be due to a number of factors, which may not indicate a need for withdrawal, and so have not included this within the bullet points.
College of Mental Health Pharmacy	Guideline	014	013-017	Suggest these are deleted unless qualified, as there are many "support groups" that should not be recommended.	Thank you for your comment. We are unable to endorse specific resources in the guideline as these will vary locally and provision can change. Evidence suggested that some people may find this useful however, and the recommendation highlights that these should be suitable for the person.
College of Mental Healt	Guideline	014	005	Unclear why anticholinergic specifically mentioned – perhaps consider others e.g. impact upon serotonin levels. Also in the case of GABA e.g. benzos/z-drugs where withdrawals	Thank you for your comment. On consideration, anticholinergic has been removed from the suggested examples. However, we are unclear on the evidence for impact on serotonin levels and so have not added this and

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h Pharmacy				may be severe and life threatening in significant dependency.	note that the recommendations guiding safe dose reduction include all medicines including benzodiazepines and Z-drugs.
College of Mental Health Pharmacy	Guideline	014	011	We would recommend that clearer guidelines are provided for the minimum options for withdrawal that should be available for each drug, regardless of location or stage of treatment, and a clear outline of what patients are entitled to, including psycho-social options because this is so critical to care provision.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that a healthcare professional can follow but enables flexibility in approach. Recommendations are included to consider providing details of sources of peer support, national and local support groups and helplines for people who are withdrawing from a medicine, and there was also evidence to recommend considering group cognitive behavioural therapy (CBT) to support people to manage symptoms when withdrawing from a benzodiazepine. There was insufficient evidence for interventions to support withdrawal from other medicines or

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					for other interventions, but research recommendations have been included on this.
College of Mental Health Pharmacy	Guideline	014	012	Replace "give2 with "offer"	Thank you for your comment. The committee's view is that the information should be given to everyone. As well as verbally the information should also be given in a format that people can read later as sometimes people may want time to think things through, or they may not be able to take it in at the time of the consultation. This does not override shared decision making or patient choice as they person can choose what to do with this information.
College of Mental Health Pharmacy	Guideline	015	006	Please provide some worked examples of reducing schedules, or direct the reader to some. And supporting resources e.g. the Orange Guide.	The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that guides dose reduction but enables flexibility in approach, and does not imply that dose reduction always has to follow a

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					predefined trajectory, as that may not always be the most clinically appropriate approach for the person. NICE guidelines follow methodology set out in the NICE guidelines manual. If other guidance is incorporated it must meet the same methodological criteria as set out in the methods manual, and the protocols relevant to the review question. An additional recommendation has been added to acknowledge use of published withdrawal schedules but notes that if used these should be applied flexibly.
College of Mental Health Pharmacy	Guideline	015	006	There needs to be far more drug-by-drug specific detail in this section as the guidance provided is quite high-level and broad. If it is not feasible provide more detailed guidelines, we would recommend the guidance signpost to other resources such as https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse and https://www.benzo.org.uk/manual/ and the RCGP Factsheets: https://www.sldtraining.co.uk/courses/resources	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the

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					recommendations do describe a schedule that guides dose reduction but enables flexibility in approach. NICE guidelines follow methodology set out in the NICE guidelines manual. If other guidance is incorporated it must meet the same methodological criteria as set out in the methods manual, and the protocols relevant to the review question.
College of Mental Health Pharmacy	Guideline	016	020	Suggest deleting. We are not aware of any such services. And these are not routinely available nationally. Conversely most substance misuse/addiction services have been drastically cut over the past decade and the third sector providers do not offer treatment packages for benzodiazepine addiction or other non-opiate addictions. There is a risk that this recommendation potentially pushes people to the unregulated talking therapies.	Thank you for your comment. This research recommendation is included because the evidence on these was too limited to inform recommendations. The committees experience was that some other psychological therapies may be of benefit, but there was insufficient evidence at presence. This therefore has not been recommended, but further research may help inform future updates of this guideline which may in turn impact service provision.
College of Mental Health Pharmacy	Guideline	017	002	Delete "exceptional". Please add a comment about whether this is due to lack of capacity eg in palliative care. Or refusal due to drug-seeking behaviours (addiction and craving) and outline how to handle these two very different scenarios .	Thank you for your comment. On consideration of stakeholder comments received and review of this recommendation the term 'exceptional circumstances' has been removed from this recommendation. Please note, use of opioids for end-of-life care is excluded from this guideline. This recommendation applies if continued use is not in the person's best interest, but the person does not want to withdraw which may be for various reasons. A

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					separate recommendation is included if withdrawal has been unsuccessful, and prescribing has to be continued.
College of Mental Health Pharmacy	Guideline	Page 17	017	Please emphasise the need for effective team working and communication between teams and services.	Thank you for your comment. The recommendations on working with other healthcare professions have been edited following stakeholder comments.
College of Mental Health Pharmacy	Guideline	018	002	We would recommend that research is also carried out into the gaps of care that exist within the system, especially the gap caused by commissioning that often leads to a disconnect between prescribing and delivery; such research would enable us to better understand the size of the issue.	Thank you for your comment. This was not a specific review question that was considered in the guideline and therefore a research recommendation has not been included in the guideline.
College of Mental Health Pharmacy	Guideline	023	028	Please review use of the term "drug-misuse disorder" as this is a contested term. Consider changing "alcohol-use disorder or drug-misuse disorder" to e.g. "problematic substance use".	Thank you for your comment. The committee are aware various terms and definitions are used and there is debate about them, however, those used in the recommendations were considered the most appropriate descriptive terms in the context they are used.

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College of Mental Health Pharmacy	Guideline	024	001	Please change "drug misuse" to "drug use".	Thank you for your comment. The committee are aware various terms and definitions are used and there is debate about them, however, those used in the recommendations were considered the most appropriate descriptive terms in the context they are used.
Company Chemists Association Ltd	Guideline	003	018 - 021	This section outlines the distinction between dependence and addiction and notes that the terms are used interchangeably. However, it is important to note that clinicians reviewing patients who are dependent on prescribed medications should not be referred to as 'addicts' or being 'addicted' as this language carries stigma and may be a barrier to safe withdrawal.	Thank you for your comment. The committee agree and included a recommendation to state that healthcare professionals should be sensitive to the use of terminology that may apportion blame to the person or be perceived adversely.
Company Chemists Association Ltd	Guideline	003	022 - 025	The guidance states that people using medicines as safe doses may also have some features of dependence, and this does not mean that treatment will be stopped. It may be helpful to clarify that dose rates do not indicate safe prescribing as many of the drugs that this guideline covers should only be initiated for short periods while other means of treatment are explored. Additionally, it may be helpful to	Thank you for your comment. This section has been reworded. People taking opioids for cancer pain were excluded from the guideline. This is stated in the scope, methods and in the review protocols for each review as well as being included in the text that will appear on the main webpage for the guideline.

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				include cancer patients in the exclusion category.	
Company Chemists Association Ltd	Guideline	003	029 - 030	We are concerned that the implication that '*people with a dependence on prescribed medicines may be reluctant to attend addiction services or seek help from their healthcare professionals because of a perceived association with illegal drug use or alcohol dependence'* places the burden of responsibility regarding prescribed drugs on the patient. Many patients will trust that their prescription is safe and will take as directed without question. Moreover, addiction services are unlikely to suitable for patients dependent on the categories of drugs covered by these guidelines. Patients require psycho-social interventions and referrals to services that may address the root cause of the issues. E.g. therapy, exercise, physical therapy.	Thank you for your comment. This section is provided for context, to explain why the guideline is needed. We agree that people taking prescription medicines are doing so because they have taken advice from a healthcare professional to do so, and include recommendations to that effect. This guideline sets out recommendations for the NHS and therefore does not assume that addiction services are the correct place for people to be seeking help, but instead focusses on how risk problems from prescribed medicines can be minimised and if necessary managed, within NHS care. We have removed the term 'addiction services' from the context so as to not imply this.
Company Chemists Association Ltd	Guideline	004	003 - 007	We are supportive of the production of evidence-based advice around dependence and withdrawal to meet a gap in guidelines in this area. However, we have concerns that the guidelines do not give enough detailed advice on how to withdraw patients (e.g. how to taper, taper duration and dose reductions).	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They made recommendations to guide the general principles of safe

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					dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that recommendations do guide dose reduction, but enable flexibility in approach. The committee agreed that a key factor was the rate of reduction of any of the medicines included in the guideline should be acceptable for the person, and there should be regular review and flexibility in the schedule to adapt this as needed. This is all reflected in the recommendations.
Company Chemists Association Ltd	Guideline	007	020 – 029	We support the detail provided in the management plan and suggest that patients should be introduced to withdrawal plan strategies at the same time as initiation. This will help to empower the patient and reinforce that these medications are intended for short durations. Information on withdrawal plans which are accessible to patients can be found on the RCP website – https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants	Thank you for your comment and for this information.
Company Chem	Guideline	007	001 - 008	We are supportive of the information and support for patients listed in the draft guideline. We suggest including information about the	Thank you for your comment. The efficacy of medicines for specific conditions is outside of the scope for this guideline

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ists Association Ltd				efficacy of medications (e.g. myth busting that pain 'killers' can make patients pain free) and the limitations of safe prescription length. Further details are required in the guidance on how dependence and withdrawal symptoms present. Not all clinicians will have experience in this area and will need the detail before they can use their clinical judgement to support patients. Details on symptoms for each drug type to the level provided by the Royal College of Psychiatrists (RCP) would be helpful – https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants	and is covered in condition NICE specific guidelines, for example the NICE guideline for chronic pain. The committee discussed including detail about the prescription length, however, they agreed that the appropriate length of each prescription would vary according to medicine and the condition being treated, and therefore it would not be helpful to provide a recommendation specifying within this guideline. However, they did agree it was important to include this detail within the management plan that was agreed and given to the person when being prescribed a medicine. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to

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					highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary.
Company Chemists Association Ltd	Guideline	008	010–-011	We are concerned that, without further detail, the advice to check whether dosage may be increased safely does not account for tolerance, therefore indicating that the medication is no longer appropriate. Additionally, the regular reviews should address how long the patient has been prescribed a certain medication and whether this is in line with official guidelines.	Thank you for your comment. The recommendation has been edited to clarify that if a satisfactory response to a medicine is achieved but subsequently lost, this may be for a number of reasons including tolerance, and in that circumstance medicines should not be automatically escalated. The guideline includes recommendations on the content of reviews. Recommendation 1.4.5 states that the decision to continue, adjust the dose or stop should be based on benefits and harms, and signs they are developing problems with dependence and the persons preference. This is also covered within the NICE guidelines for Medicines adherence and Medicines optimisation which are cross-referred to in the section for reviewing medicines.
Company Chemists Association Ltd	Guideline	010	007–-012	We agree that *Pharmacists in primary care may play a key role in supporting prescribing* however, community pharmacists have the most interactions with the majority of patients across the health care system because they dispense medicines to patients. Therefore, the role of appropriately trained community pharmacists	Thank you for your comment. Community pharmacists are considered to sit within primary care, and therefore this recommendation equally applies to them. The committee agree that this guideline may also be relevant for over-the-counter medicines, however, it is beyond NICE's

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				should be included in these guidelines as there is a key opportunity to undertake an intervention with patients at the point of supply. Furthermore, the need for access to shared records is well documented and more work is needed by commissioner to invest so that pharmacists can see relevant information from the prescriber but to also enable pharmacists to write to the record so that the prescriber can be kept informed about reviews, withdrawal programmes, emergency supply requests and any other important information. This may also be helpful with regards to the sale and supply of over-the-counter medicines including such medicines that contain dependence forming ingredients such as codeine. Furthermore, it may be helpful to include a recommendation on whether medicines that induce dependence are suitable for electronic repeat dispensing (eRD) which potentially reduces the amount of contact the patient has with GP prescribers and can exacerbate longer prescription lengths.	remit to make recommendations on the sale and supply of over-the-counter products. The evidence reviewed did not inform recommendations on electronic repeat dispensing practices. However, the committee did agree it was important to state the length of each prescription in the management plan, and for the frequency of reviews to reflect this.
Company Chemists Assoc	Guideline	012	008 - 015	We believe that prescription duration should be included. If the prescription duration has exceeded official guidelines then that should be a flag for review.	Thank you for your comment. The committee discussed possible recommendations for prescription amounts and length however, there was no evidence identified to inform specific recommendations on this, and the committee agreed this would vary according to medicine and condition. They

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iation Ltd					agreed that prescription length should reflect the management plan (including plans for review), controlled drugs guidance and relevant legislation. Recommendation 1.3.5 has been amended to state that the duration of each the prescription that will be issued should be included in the management plan. The prescribing strategies recommendations refer back to this noting that prescribing should be consistent with the management plan. The committee agreed it was not possible to make recommendation on specific volumes or duration of prescriptions as this would vary between medicines, however, they do agree it is important to consider at each review.
Company Chemists Association Ltd	Guideline	012	019 - 023	It is worth noting that patients may not be in a position to recognise that problems they are facing or symptoms are as a result of either their medication (i.e. side effects) or as a result of dependence. The clinician will need to use their consultation skills to initiate a discussion that is open and free from stigma.	Thank you for your comment. The committee agree that these discussions can be difficult, particularly when a person is in distress. This recommendation was included to address this. The recommendations for supporting people also include asking people whether they would like to have support during appointments from a family member, carer or other person close to them. This applies throughout and would be of relevance when making decisions to withdraw from medicines.
Company Chem	Guideline	013 014 015	018 – 030	We are concerned that the withdrawal guidelines are influenced by other measures such as SMART goals which may not always be	Thank you for your comment. The committee agree with the points you raise and believe the recommendations reflect a slow dose reduction schedule that is acceptable to the

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ists Association Ltd		016	001 – 009 029 – 030 001 - 007	appropriate for these classes of medications. Patients should be empowered to reduce at their own speed, and should not be encouraged to reduce at speed or stop abruptly. This can cause severe negative side effects, which can also resemble a relapse of the condition the medication was originally prescribed for. Therefore, more detail is needed on withdrawal symptoms for both clinicians and patients. The RCP goes into detail about this in relation to anti-depressants (see https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants) and there are other sources of available guidance that go into detail about the other categories of drugs. We understand that NICE may not have included these sources because they constitute 'grey literature' - however, it is imperative that the standard of patient care is put first and prioritised over a strict guidance drafting principles.	person and has flexibility to be adapted according to their experience of withdrawal or changing circumstances. The committee also agree that empowering the person to control their dose reduction is important and can be helpful for some people. A statement was included in the recommendation for dose reduction to consider giving individuals additional control over the process of dose reduction, to reflect this. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that

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					would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary.
Company Chemists Association Ltd	Guideline	015	024 - 025	*During withdrawal, offer continued management of the underlying condition for which the medicine was prescribed, if needed* We suggest that it is important that holistic and alternative therapies are explored, and they will likely require referral to other services as support will sit outside of the skillset of the prescriber (e.g. talking therapies, peer support groups, bereavement counselling, chiropractors, physiotherapists)	Thank you for your comment. Management of specific conditions these medicines are used for is outside of the scope for this guideline. Condition specific NICE guidelines should be followed, where available, including non-pharmacological options.
Company Chemists Association Ltd	Guideline	016	019 – 026	*Interventions to support withdrawal* In this section, there are two things not to do but there is little guidance on interventions and intervention methods, beyond group cognitive behavioural therapy for a benzodiazepine.	Thank you for your comment. The evidence for interventions to support withdrawal was too limited to inform recommendations. The committee consider that there may be other approaches that could be beneficial, and so a number of research recommendations were included on this topic to help inform future updates of this guideline. The committee's view was that recommendations to agree a slow, individualised, flexible dose reduction would help minimise problems with withdrawal.

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Company Chemists Association Ltd	Guideline	017	001 - 023	The guideline needs to include more practical steps on dose reduction ('tapering') to address basic slow tapering information in its upcoming guideline on Safe Prescribing and Withdrawal Management, to include information on tapering rates, the interval between dose reductions, how to reduce doses and the overall duration of taper.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendation does describe a dose reduction schedule but also enables flexibility in approach.
Company Chemists Association Ltd	Guideline	017	009 - 016	In addition to the advice that some patients may find a reduction schedule tolerable, and others may find the same schedule harmful, it would be helpful to include information on metabolic tapering. Again, this may be contained in the 'grey literature' - however, this is an important area for patient-centred support.	Thank you for your comment. Evidence reviewed did not inform recommendations on metabolic tapering, however.
Connect Health	Guideline	General	General	Connect Health thought generally that the guidelines were well balanced and based on good evidence.	Thank you for your comment.

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Connect Health	Guideline	General	General	It would be useful to signpost to NICE guidelines for the psychological treatment of depression and anxiety disorders in the context of drug withdrawal. As it is often the case that there are complex biopsychosocial factors interplaying which may impact the ability of the individual to withdraw from a medication.	Thank you for your comment. The guideline includes a cross-reference to the NICE guideline for depression. The committee agreed that the general principles of withdrawal in this guideline apply for this population and are consistent with the current recommendations in that guidance. The NICE guideline for generalised anxiety disorder and panic disorder does not include recommendations on dose reduction or drug withdrawal.
Connect Health	Guideline	024	015	Modified release vs standard release. Opinion was divided in Connect Health regarding the comment that standard release opioids are less frequently associated with problems compared with modified release opioids and transdermal preparations. Is this comment because modified release and transdermal preparations are generally more potent?	Thank you for your comment. This was informed by the evidence review of risk factors associated with dependence which the committee agreed was consistent with their clinical experience. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise.
Connect Health	Guideline	029	025 - 026	A guide to a starting point for a dose reduction would be helpful especially for non-experts. The Faculty of Pain Medicine suggest a taper by 10% weekly or two weekly.	The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations

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					are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendation does describe a dose reduction schedule but also enables flexibility in approach.
Connect Health	Guideline	029	022	Dose reduction. Can a comment be made on when reducing opioids, would it be preferable to remain on the same preparation and gradually reduce regardless of whether it is standard release, modified release, or transdermal preparation. Or is there a recommendation for ease of reducing an opioid which preparation would be best to use.	Thank you for your comment. Evidence did not inform a recommendation on different opioid preparations during withdrawal.
Connect Health	Guideline	029	030	For gabapentinoids, the dose can be reduced by a fixed amount at each decrement. What is the rationale for this? From experience dose reductions off gabapentinoids can be as difficult as opioids therefore the rate of reduction may need to modified.	Thank you for your comment. This recommendation was formed by committee experience and knowledge of PHE and NHS reports on safe use of gabapentinoids, as well as the summary of product characteristics (SPC) guidance on tapering. These all recommend reducing by fixed amounts. In the committees experience most schedules are slower than the manufacturers recommendations in the SPC to minimise withdrawal and re-emergence of symptoms.
Department of	Guideline	General	General	OHID's Addiction and Inclusion Directorate welcomes the draft guideline, and its comprehensive recommendations, underpinned	Thank you for your comment.

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Health and Social Care				– as NICE acknowledges it is – by the prescribed medicines review of the directorate's forerunner in Public Health England.	
Department of Health and Social Care	Guideline	001	(Box)	The guideline needs to be specified as not applying to the specialist treatment of illicit drug or alcohol dependence. The treatment of opioid dependence, especially, usually involves use of an opioid substitution medicine (itself associated with dependence or withdrawal) that may need to be prescribed rapidly to prevent risk of further harm, without all the cautions and caveats rightly recommended by the draft guideline for preventing and treating inadvertent dependence on medicines. Although less common, similar is true of other illicit drug and alcohol dependence treatment. Applying all the otherwise sensible recommendations of the draft guideline in these cases would result in unacceptable delays to starting treatment. So, we suggest adding to the last line of the first box para something along the following lines: "The guideline does not cover use of opioids prescribed for acute pain, cancer pain or at the end of life, or for the specialist treatment of illicit drug or alcohol dependence." And include this	Thank you for your comment. This is stated in the scope, the methods chapter that accompanies the guideline and the review protocols for each question. This is also clarified at the beginning of the guideline where the text refers to prescribed medicines only. It will also be added to the guideline overview page on publication.

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				addition wherever else the limit of the guideline is discussed. This exclusion would align the guideline with its own reference to being "underpinned" by Public Health England's report [on] … the scale, distribution and causes of prescription drug dependence and what might be done to address it. That report was itself clear that it was not about illicit drug misuse and dependence, and their treatment.	
East and Central Brighton PCN	Guideline	003	011-015	Do not like that this could easily be misinterpreted by clinicians & patients alike...'may continue to be prescribed for various reasons'. 'can provide lasting symptom management for a proportion of people'	Thank you for your comment. This section has been reworded to reduce possibility of misinterpretation and we have provided examples of when continued prescribing may occur.
East and Central Brighton PCN	Guideline	005	014	Risk factor for problems says 'opioid + BZD' – what about gabapentinoids zdrugs?	Thank you for your comment. Evidence reviewed specifically highlighted there being a risk of problems associated with dependence for people concurrently taking and opioid and a benzodiazepine. There was very limited evidence of the risk with concurrent use of pregabalin or gabapentin. Although this also demonstrated an increased risk, the evidence for concurrent use of gabapentinoids in people prescribed opioids was from a single study and of low quality and therefore not considered sufficient to inform a

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					recommendation. The discussion of this evidence is detailed in evidence review E.
East and Central Brighton PCN	Guideline	005	017	Avoid mr opioids – do you therefore recommend IR opioids alone? Is this not more risky?	Thank you for your comment. The recommendation to avoid using modified release opioids was informed by the evidence review of risk factors associated with dependence. It is acknowledged that the evidence had limitations, however the committee agreed that it was from a relatively large cohort and was consistent with their clinical experience. The committee do not agree that immediate release, or standard release alone is riskier. In their experience, people on standard release opioid regimens tend to use lower average opioid doses (and are therefore exposed to fewer harms) than those on fixed dose modified release regimens. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise. Recommendations to perform benefit-harm assessment and to make a shared decision with the person still apply.

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East and Central Brighton PCN	Guideline	010	001-006	What if primary care disagrees with secondary care eg around long term prescribing of BZDs or high dose opioids–- primary care are legally responsible for their prescribing therefore are they ok to refuse? This is a constant issue for primary care – takes up a LOT of our time.	Thank you for your comment. The committee agree this is an important situation to acknowledge and included a recommendation for what to do if the prescriber does not think this is in the person's best interests. This includes stating that 'the prescriber should not prescribe a medicine if they believe it is not in the person's best interest'.
Faculty of Pain Medicine of the Royal College of Anaesthetists	Guideline	General	General	We note there is no mention of timing and acute events. When a patient is presenting with a flare up of their known chronic pain or a new acute pain on a back ground of chronic pain it is often not the time to start the weaning process. It can be used as a 'teachable moment' and to get the ball rolling to start the weaning process once the acute episode has settled.	Thank you for your comment. The committee agree that individual circumstances (which may include a flare up of pain) are important to consider when making a shared decision to start withdrawing. This is acknowledged in the final bullet of the recommendation highlighting factors to take into account when planning withdrawal: "factors that might influence the timing of the start of the dose reduction, such as the person's circumstances and available support."
Faculty of Pain Medicine of the Royal Colle	Guideline	General	General	The Faculty are pleased to see the development of this helpful and long over-due guidance. We are pleased to see that NICE have taken on qualitative methodologies to underpin this work and that it is very balanced throughout. Overall the outcomes triangulate with clinical experience and expert opinion on best practice, which is very reassuring, especially given other	Thank you for your comment.

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ge of Anaesthetists				publications in pain which have created confusion and concerns over patient safety.	
Faculty of Pain Medicine of the Royal College of Anaesthetists	Guideline	015	6-23	Recommendation 1.5.10 includes the following *consider giving the person an element of control over the process of dose reduction (for example, by issuing their usual prescription for a month and encouraging them to reduce the dose by their chosen decrements, rather than issuing successive reduced prescriptions)* Further information on how a person who successfully reduces the dose should manage / dispose of " surplus " medication might be useful here to emphasise safe and responsible prescribing and use.	Thank you for your comment. This recommendation has been reworded to clarify how this might be carried out.
Faculty of Pain Medicine of the Royal College of Anaes	Guideline	018	9-12	We particularly welcome research recommendations 2. **Psychological interventions to support withdrawal** and 'other' : **Acupuncture to support withdrawal from opioids.** Evidence on this is much needed.	Thank you for your comment.

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Grunenthal Ltd	Guideline	General	General	It may be supportive to end users of this Guideline if the title is amended to mention 'chronic or long term' conditions, e.g. "Medicines associated with dependence or withdrawal: safe prescribing and withdrawal management for adults with chronic or complex conditions"	Thank you for your comment. The scope of this guideline, as well as the review protocols and methods chapter, state the population that this guideline applies to, noting that use of opioids for acute pain is excluded. However, otherwise the guideline is not limited to chronic or complex conditions.
Grunenthal Ltd	Guideline	General	General	We welcome this guideline and we agree that risk factors which may increase an individual's potential to develop dependence to opioids or benzodiazepines should be carefully assessed and considered when making prescribing decisions. Treatment should be tailored to individual needs. Further education around risk factors and association with the development of dependence may need to be stressed for both the prescriber and the patient, for example mental health disorders, alcohol disorders, previous drug mis-use. We strongly agree that the needs of the individual should be taken into account when balancing the benefit and harm and these factors should not be seen as barriers to prescribe if an opioid or benzodiazepine is the most appropriate treatment to aid the individual in the management of their chronic condition.	Thank you for your comment. The committee agree that it is important that factors that are associated with an increased risk of problems associated with dependence in isolation should not be barriers to prescribing. This was stated in the rationale, but this has now been added to the recommendation to ensure that is clear.

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Grunenthal Ltd	Guideline	General	General	We agree that, as the committee has recommended, an overall benefit- harm assessment should be performed in collaboration with the patient, to appropriately prescribe a treatment that will support the individual to achieve a treatment goal. We would urge the committee to apply the same recommendation to the use of modified release or long acting tablets. The proposed guideline states that 'modified release formulations' should be avoided. We urge the committee to reconsider this recommendation and wording. These licensed products have proven efficacy and safety in the management of chronic conditions for which they are approved. A recommendation to 'avoid' these products may not be in the best interest of patients. The recommendation here should be brought in line with the overall guidance to perform a benefit-harm assessment in collaboration with the patient to appropriately prescribe a treatment that will support the individual to achieve a treatment goal, with regular reviews agreed. We would like to put forward the following arguments against the recommendation to 'avoid the use of modified release formulations'.	Thank you for your comment. The recommendation to avoid using modified release opioids was informed by the evidence review of risk factors associated with dependence. It is acknowledged that the evidence had limitations however, the committee agreed that it was from a relatively large cohort and was consistent with their clinical experience. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise. Recommendations to perform benefit-harm assessment and to make a shared decision with the person still apply. The inclusion of this consideration in the recommendation is not limiting medicines, it is highlighting things to consider, including the appropriate choice of medicine formulation for the person, to minimise problems associated with dependence.

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				• The studies included within the evidence review on the risk factors for dependence which underpin this recommendation are of a low quality grade with a high or very high risk of bias as per the QUIPS checklist. • In addition, there is only one cohort study which specifically investigated long-acting opioids vs short acting opioids for predicting opioid abuse or dependence (HR 2.17) (Very low quality and serious risk of bias). A single study provides insufficient quantity of data from which to draw conclusions. • It should be noted that all studies included in table 59 of the evidence review have been downgraded due to serious indirectness as the proportion of those treated for 'chronic pain' was unclear. Critically, Public Health England recommend ' Inappropriate limiting of medicines may increase harm, including the risk of suicide, and lead some people to seek medicines from illicit or less-regulated sources, such as online pharmacies.'	

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				We strongly suggest that the committee remove this recommendation and replace it with a recommendation for more robust, high quality research.	
Grunenthal Ltd	Guideline	General	General	We would like to draw attention to the Public Health England Report on Prescribed Medicines (Dec 2020). Prescribed medicines review: summary - GOV.UK (www.gov.uk). In line with the NICE chronic pain guidance, the focus for the management of chronic conditions should be effective, personalised care. Care should include shared decision making with patients and regular reviews of whether treatment is working. Patients who want to stop using a medicine must be able to access appropriate medical advice and treatment must never be stigmatised. Critically, Public Health England recommend 'Inappropriate limiting of medicines may increase harm, including the risk of suicide, and lead some people to seek medicines from illicit or less-regulated sources, such as online pharmacies.' There have been very few high-quality research studies on medicine dependence and withdrawal, and their prevention and treatment, in the past 10 years. More research is required.	Thank you for your comment. The committee are aware of the Public Health England (PHE) Report on Prescribed Medicines. The relevant evidence reviews and review protocols (from the PHE report) were used to help inform the reviews undertaken in this guideline, with adaptations to widen the searches to cover all years and counties. The search results from relevant PHE report reviews were also assessed for inclusion where they had not been picked up in the revised searches used for the guideline reviews to ensure all relevant studies were taken into account. The committee consider that the guideline is consistent with the relevant recommendations made in the PHE report. A number of research recommendations have been made within this guideline highlighting particular areas in which evidence is lacking that would help inform future updates of this guideline.

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Grunenthal Ltd	Guideline	003	009	We would ask that consideration is given to providing further clarity to the statement "It also covers medicines that were initially prescribed for acute pain but continue to be prescribed over a longer term". It would be good to understand whether this applies to conditions that may be acute at onset and progress to a chronic state or is this statement referring to lack of appropriate follow up of patients (patients initiated on medicines with a high risk of addiction/ dependence and who remain on these medicines without timely review).	Thank you for your comment. This statement has been included to acknowledge both of the scenarios that you suggest, recognising that if someone is using opioids and has developed problems associated with dependence, these recommendations may still apply irrespective of how their use began. However, prescribing opioids for acute pain is not covered within this guideline.
Grunenthal Ltd	Guideline	005	016-018	The proposed guideline states that 'modified release formulations' should be avoided. We urge the committee to reconsider this recommendation and wording. These licensed products have proven efficacy and safety in the management of chronic conditions for which they are approved. A recommendation to 'avoid' these products may not be in the best interest of patients. The recommendation here should be brought in line with the overall guidance to perform a benefit-harm assessment in collaboration with the patient to appropriately prescribe a treatment that will support the individual to achieve a treatment goal, with regular reviews agreed.	Thank you for your comment. This was informed by the evidence review of risk factors associated with dependence. It is acknowledged that the evidence had limitations however, the committee agreed that it was from a relatively large cohort and was consistent with their clinical experience. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise. Recommendations to perform benefit-harm

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				We would like to put forward the following arguments against the recommendation to 'avoid the use of modified release formulations'. •The studies included within the evidence review on the risk factors for dependence which underpin this recommendation are of a low quality grade with a high or very high risk of bias as per the QUIPS checklist. •In addition, there is only one cohort study which specifically investigated long-acting opioids vs short acting opioids for predicting opioid abuse or dependence (HR 2.17) (Very low quality and serious risk of bias). A single study provides insufficient quantity of data from which to draw conclusions. •It should be noted that all studies included in table 59 of the evidence review have been downgraded due to serious indirectness as the proportion of those treated for 'chronic pain' was unclear. Critically, Public Health England recommend ' Inappropriate limiting of medicines may increase harm, including the risk of suicide, and lead some people to seek medicines from illicit or less-regulated sources, such as online pharmacies.' We strongly suggest that the committee remove this recommendation and replace it with a	assessment and to make a shared decision with the person still apply. The inclusion of this consideration in the recommendation is not limiting medicines, it is highlighting things to consider, including the appropriate choice of medicine formulation for the person, to minimise problems associated with dependence.

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				recommendation for more robust, high quality research.	
Grunenthal Ltd	Guideline	011	21-023	We would recommend that reference is made throughout the document to "tapering" the medication, in addition to the language of continuing or stopping. The statement would then read "During the review, discuss the benefits and risks of continuing, tapering or stopping the medicine with the person. Base the decision to continue, taper or stop on this discussion….."	Thank you for your comment. Although tapering is a term considered by healthcare professionals and people working in related areas, it may not be so well understood by lay readers of the guideline. Therefore, the recommendations use the terms 'dose reduction', 'stopping' and 'withdrawal'.
Grunenthal Ltd	Guideline	013	018	We would recommend that the term "tapering" is used rather than "Gradual withdrawal of medicine"	Thank you for your comment. Although tapering is a term considered by healthcare professionals and people working in related areas, it may not be so well understood by lay readers of the guideline. Therefore, the recommendations use the terms 'dose reduction', 'stopping' and 'withdrawal'.
Grunenthal Ltd	Guideline	023	023	The guidance explains that the recommendation is based on the committee's experience and evidence showing a dose-response association between higher doses of opioids and incident addiction to opioids when taken long term. It is worth noting that whilst the guidance is for 'chronic pain' it also covers medicines that were initially prescribed for acute pain but continued to be prescribed over a longer term. We suggest to amend the wording to 'start with the lowest	Thank you for your comment. The committee discussed the best terminology to use in this recommendation, however, they considered that until the person had tried the medicine you could not know what the lowest effective dose would be. Therefore, the term low dose was used instead.

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				effective dosage' rather than 'low' dose' throughout the document. Rationale: This would be in-keeping with existing guidance and recommendations regarding opioid trials and 'start low, go slow' initiation of opioids. NICE guidance on prescribing of controlled drugs advises that HCPs should 'check the persons' current clinical needs and if appropriate, adjust the dose until a good balance is achieved between benefit and harms (Recommendations | Controlled drugs: safe use and management | Guidance | NICE); DHHS guideline: RECOMMENDATION 2C: The type, dose, and duration of opioid therapy should be determined by treating clinicians according to the individual patient's pain condition while using the opioid medication at the lowest effective dosage and shortest duration appropriate to achieve adequate pain control for improved function and QOL. pmtf-final-report-2019-05-23.pdf (hhs.gov); GMC guidance – point 61 in reference to controlled drugs: HCPs should provide a limited quantity and dose- one that is sufficient to make sure that the patient received suitable care. A change to this wording would also support the appropriate use of medicines, within license.	

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Grunenthal Ltd	Guideline	024	013-017	With respect to the statement "Evidence and the committee's experience also showed that standard-release opioids are less frequently associated with problems compared with modified-release opioids", we would like to point out that this is inconsistent with the body of evidence from published literature that showed that in particular fast pharmacokinetics (i.e. short Tmax, high Cmax) is associated with high drug-liking and thereby promotes the development of drug abuse and dependence e.g. Shram et al. Journal of Clinical Psycopharmacology:2010; 30(1); 25-33. The proposed guideline states that 'modified release formulations' should be avoided. We urge the committee to reconsider this recommendation and wording. These licensed products have proven efficacy and safety in the management of chronic conditions for which they are approved. A recommendation to 'avoid' these products may not be in the best interest of patients. The recommendation here should be brought in line with the overall guidance to perform a benefit-harm assessment in collaboration with the patient to appropriately prescribe a treatment that will support the individual to achieve a treatment goal, with regular reviews agreed.	Thank you for your comment. This was informed by the evidence review of risk factors associated with dependence. It is acknowledged that the evidence had limitations however, the committee agreed that it was from a relatively large cohort and was consistent with their clinical experience. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be appropriate for everyone. The rationale for this recommendation now states that this is unless clinical considerations or the persons circumstances dictate otherwise. The inclusion of this consideration in the recommendation is not limiting medicines, it is highlighting things to consider, including the appropriate choice of medicine formulation for the person, to minimise problems associated with dependence. The references you have provided were not relevant to include within any of the guideline evidence reviews (neither the review for risk factors or prescribing strategies) and therefore we are unable to comment on their conclusions.

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				We would like to put forward the following arguments against the recommendation to 'avoid the use of modified release formulations'. •The studies included within the evidence review on the risk factors for dependence which underpin this recommendation are of a low quality grade with a high or very high risk of bias as per the QUIPS checklist. •In addition, there is only one cohort study which specifically investigated long-acting opioids vs short acting opioids for predicting opioid abuse or dependence (HR 2.17) (Very low quality and serious risk of bias). A single study provides insufficient quantity of data from which to draw conclusions. •It should be noted that all studies included in table 59 of the evidence review have been downgraded due to serious indirectness as the proportion of those treated for 'chronic pain' was unclear. Critically, Public Health England recommend ' Inappropriate limiting of medicines may increase harm, including the risk of suicide, and lead some people to seek medicines from illicit or less-regulated sources, such as online pharmacies.' We strongly suggest that the committee remove this recommendation and replace it with a	

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				recommendation for more robust, high quality research.	
Grunenthal Ltd	Guideline	029	023	We believe that in addition to the information here it would be worth stating that many of these drugs have very clear starting dose, titration and tapering information in their labels, which should be referenced for safety. It is very difficult to make one statement that covers all of the treatments covered within this guidance, so reference to the specific label information should be advised.	Thank you for your comment. The committee considered that this information is already available within the BNF and SPC for the medicine. However, they note that starting at a low dose is associated with lower risk of problems associated with dependence.
Humankind	Guideline	General	General	We welcome NICE's creation of guidelines regarding medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults. However, we believe that the draft guidance only touches the tip of what needs to be created. The guidelines have been long awaited by the sector since the publication of the PHE evidence review in 2019 but the draft that has been published lacks detail and does not go deep enough in providing specific guidelines for different professions, medicines or settings. In our following comments, we highlight the guidelines that we believe need further detail or expansion.	Thank you for your comment. The recommendations are based on the best available evidence. In many cases the committee agreed the evidence informed recommendations for general principles that applied to all medicine classes within the guideline scope and that the most important factor was an individualised approach tailored to the persons circumstances. Where evidence suggested separate recommendations should be made for particular classes of drugs, separate recommendations have been made. Responses to your specific comments have been provided below.

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Humankind	Guideline	General	General	Whilst it is positive to see a multidisciplinary committee, it is disappointing that - given the focus on medicines -there was not a higher number of pharmacists include in the consultation. Furthermore, it may have been beneficial to include a specialist pharmacist with expertise regarding mental health and addiction management.	Thank you for your comment. The guideline committee composition was agreed during the scoping for the guideline and represents the range of disciplines considered necessary to address the breadth of the scope. It was agreed that a pharmacist with expertise in the field of safe prescribing and withdrawal management was required, not specifically one the expertise in mental health and addiction management although that would not have precluded someone with such expertise being appointed. Candidates were appointed following interview, according to their suitability and expertise relevant to the guideline scope.
Humankind	Guideline	General	General	The guidelines do not make reference regarding out-of-hours support or access to emergency supplies; we would recommend adding this in as many people may require this, especially people experiencing isolation or living in rural areas.	Thank you for your comment. Consideration of models of service provision was outside of the scope of this guideline and therefore recommendations cannot be made on out of hours support.
Humankind	Guideline	General	General	We welcome the recognition that intersecting dependencies and health issues must be included in any consideration regarding withdrawal, and encourage you to highlight this further in the guidance.	Thank you for your comment. History of problems associated with dependence has now also been added to the recommendation of factors to consider when considering withdrawal. While the committee agree that a holistic individualised approach is important throughout, health issues have not been added here as not all comorbid health conditions would lead to an increased risk of problems with withdrawal.
Humankind	Guideline	General	General	Take home naloxone provision must be considered in the context of opioids.	Thank you for your comment. The committee acknowledged that take home naloxone is used in people with known current or history of substance misuse, however, it was noted

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					that there is no evidence that this is an effective strategy for dependence on prescribed medicines, and no evidence was identified in the guideline reviews. The committee discussed that although it is a strategy that is beginning to be used in the US, there is much more cross over in the US setting of people with prescription drug dependence and substance misuse problems. Therefore, this is likely to be a context-dependent strategy that is less likely to be relevant in the UK setting. This discussion is detailed in the discussion of the evidence in evidence review B.
Humankind	Guideline	General	General	Please add more information about management of relapse including fast track into services, the risk of accidental overdose, role of harm reduction and naltrexone in the case of opioid maintenance of abstinence prescribing.	Thank you for your comment. Management of relapse was not within the scope of this guideline. Some condition-specific NICE guidelines do, however, include recommendations on this topic. The committee acknowledge that naltrexone is used for relapse in formerly illicit opioid dependent people or formerly alcohol dependent people, however, there is no evidence that this is an effective strategy for dependence on prescribed medicines, and no evidence was identified in the guideline reviews.
Humankind	Guideline	General	General	Consider strengthening the role of drug and alcohol treatment services/seeking specialist support when the prescriber is at their limit of confidence/competence including specialist pharmacist input.	Thank you for your comment. The committee considered that the recommendations in this guideline would enable safe withdrawal from the medicines in all NHS settings in which these medicines are prescribed. A recommendation has now been added highlighting that these decisions can be difficult for the prescriber as well as the patient, and note that additional time may be required to consult with colleagues.

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Humankind	Guideline	001	General	It would be helpful to state the treatment setting this relates to, e.g. for primary care, and recognise that there are further guidelines/restrictions in the secure prison estate for example.	Thank you for your comment. This guideline applies to all settings in which NHS care is provided or commissioned, as detailed in the scope.
Humankind	Guideline	003	016-025	Perhaps consider reference to International Clinical Diagnosis to strengthen the position taken/points made.	Thank you for your comment. However, NICE do not routinely include references in the context section of guidelines. A hyperlink to the ICD-11 has not been added because the definitions within the ICD are split up according to opioid dependence, sedative hypnotic, anxiolytic dependence etc. rather than providing a single definition that would be a quick reference for readers of the guideline.
Humankind	Guideline	003	011-013	We would suggest emphasising the risk benefit need – notably for antidepressants in reducing suicide risk – as it is important to avoid adding to stigma about the role of medicines for mental health wherever possible.	Thank you for your comment. The context section is intended to briefly set out the background and need for the guideline and therefore does not cover all issues related to the use of these medicines.
Humankind	Guideline	004	001-002	It would be beneficial to reference the impact of stigma here.	Thank you for your comment. This has been added.
Humankind	Guideline	005	012	Please make specific reference to drug AND alcohol use. Also, we would suggest avoiding language such as 'drug misuse' since this is a contested term in the context of illicit drug use and would suggest 'drug use' or 'problematic substance use' instead (also relevant for page 23, line 28 and page 24, line 1)	Thank you for your comment. This recommendation has now been edited to state drug or alcohol misuse. This is consistent with the evidence reviewed which suggested an increased risk in people with a history of substance misuse including both drug and alcohol misuse. The committee are aware various terms and definitions are used and there is debate about them, however, those used in the

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					recommendations were considered the most appropriate descriptive terms in the context they are used.
Humankind	Guideline	007	008	We suggest that this is rephrased, to instead emphasise practical steps that should be taken to manage discontinuation of the medication in a way that minimises adverse effects – this is especially important so as not to discourage the use of antidepressants where they are clinically indicated.	Thank you for your comment. This recommendation has now been split into 3 sections (1.3.1, 1.3.2 and 1.3.3), all are about information that should be provided when people are starting one of these medicines. The committee consider that adverse effects of medicines cannot necessarily be avoided and it is important people are made aware that these might occur. A theme also arose from a qualitative review in the guideline that people felt they were not always given enough information about possible harms of the treatment before starting, and it would be beneficial to do so. The guideline recommends steps to ensure safe prescribing of these medicines, including starting with a low dose, regular frequent reviews when starting to test efficacy, safety and acceptability, and ongoing regular reviews including consideration benefits and harms and the persons preferences. Recommendations on withdrawal of these medicines are in section 1.5. A cross reference to this section has been added to recommendation 1.3.1.
Humankind	Guideline	007	017	We strongly recommend referencing free and confidential support services provided by the third sector as well as the NHS.	Thank you for your comment. We are unable to endorse specific resources in the guideline as these will vary locally and provision can change.

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Humankind	Guideline	007	019	We would welcome an additional point about emphasising the anticipated benefits – again especially important for antidepressants – and a reference to the importance of continued psychosocial interventions alongside medication.	Thank you for your comment. The anticipated benefits is included as an item that should be included in the management plan within 'the intended outcome of treatment'. Although the committee agree that non-pharmacological treatment should always be considered, ongoing management of specific conditions is outside the scope of this guideline.
Humankind	Guideline	007	020	It would be good to add in detail about the need to access psychosocial interventions/signposting as needed	Thank you for your comment. Recommendation 1.3.2 states that the healthcare professional should consider supplementing verbal and written information with details of peer support networks or online forums suitable for the person. Further support and interventions relevant to specific conditions are outside the scope for this guideline.
Humankind	Guideline	008	005	Suggest consolidating the last two bullet points into one: to review if the dose requires changing and how to do this suited to the needs of the individual. Again, strongly recommend emphasising the importance of additional support in the form of psychosocial interventions.	Thank you for your comment. These two bullets have been combined and reworded to focus on dose adjustment. Recommendation 1.3.2 states that the healthcare professional should consider supplementing verbal and written information with details of peer support networks or online forums suitable for the person. Further support relevant to specific conditions is outside the scope for this guideline.
Humankind	Guideline	008	021	We suggest rephrasing this so that it is not just about other people living there but 'vulnerable others' e.g. visitors, including young people, as well as safe storage when transporting/outside of the home – as this is where notable learning from deaths have occurred.	Thank you for your comment. Although the committee note that vulnerable others may be of merit to consider in the recommendation, they consider that it is not just the vulnerable and have not added this. A separate consideration has been added to the recommendation of what information

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					should be given to the person when starting treatment (1.3.1) to include information on safe storage of the medicine.
Humankind	Guideline	009	001	The focus of this section is very much on prescribers, however there needs to be further consideration of other healthcare professionals who are involved in withdrawal, such as pharmacists, nurses and other clinicians who are working in recovery support settings. There is currently no clear widely-adopted process for many clinical professions in how to handle cases of people who are undergoing withdrawal management. The guidelines need to be informed by a holistic approach to ensure that everyone who is interacting with the person is taking a cohesive approach to their case.	Thank you for your comment. The committee considered there are a range of healthcare professionals who may be involved in both prescribing and supporting withdrawal from these medicines. The guideline recommendations apply to all and therefore, the terms 'prescriber' and 'healthcare professionals' have been used so as not to specify professions.
Humankind	Guideline	009	023	It would be useful to widen to pan-interface settings medicines reconciliation issues not just between secondary and primary care e.g. specialist drug and alcohol treatment services, out of hours provision and prisons (especially prison releases/out of hour requests). We'd suggest emphasising the need for shared clinical management systems and timeliness of sharing of information.	Thank you for your comment. The committee agree that the points you raise are true, however, all other recommendations in the guideline still apply to the healthcare professional in the contexts that you describe, and therefore these considerations have not been added to this recommendation.
Humankind	Guideline	010	016	Please include reference to an individualised risk management plan/safeguarding and signpost to guidance where it exists for specific	Thank you for your comment. Recommendation 1.4.4 includes a cross-reference to section on medication review in

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				meds e.g. for z-drugs and the Drug misuse and dependence: UK guidelines on clinical management Orange guide.	the NICE guideline on medicines optimisation where recommendations are made that apply for all medicines. Hyperlinks to all condition specific guidelines are not included within this guideline document, however, they will be available on the NICE website. Resources produced by other organisations are not linked to or referenced in this document unless they informed evidence reviews, or evidence demonstrated they should be recommended.
Humankind	Guideline	013	008	This section would benefit from being more explicit about the severe risks of withdrawing from some medications if not managed carefully. For example, the guidelines should make clear that sudden cessation of benzodiazepines in dependency can be fatal if inappropriately managed and therefore this should be done only in certain settings ie acute care. Also, it would be useful to cover the role of symptomatic relief in the case of opioid withdrawal. We know this is important given inappropriate management also perpetuates use despite the ongoing harms in the case of dependency.	Thank you for your comment. The committee agree that withdrawal needs to be done carefully to ensure safe withdrawal. The view of the committee is that the recommendations should focus on the need for an approach individualised to the person that should also be flexible to pause or adjust the reduction schedule as needed if withdrawal symptoms occur, circumstances change or if it's not tolerable for the person. They consider this applies across these medicines and that if withdrawn carefully harm can be avoided. Symptomatic relief is recommended when withdrawing from benzodiazepines, informed by evidence reviewed. However, for opioids symptomatic relief is only recommended as something to consider if undertaking abrupt withdrawal as the committee considered careful withdrawal is less likely to

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					require this. The recommendations do acknowledge exceptional circumstances where a more rapid withdrawal is required. In the rationale the recognise this is often done in hospital, however, there was no evidence to recommend this should always be the case.
Humankind	Guideline	014	005	We are not clear by anticholinergic is specifically mentioned here, yet other impacts are not. Perhaps consider including others such as impact upon serotonin levels and that in the case of GABA e.g. benzos/z-drugs withdrawals may be severe and life threatening for people with significant dependency.	Thank you for your comment. On consideration, anticholinergic has been removed from the suggested examples. However, we are unclear on the evidence for impact on serotonin levels and so have not added this and note that the recommendations guiding safe dose reduction include all medicines including benzodiazepines and Z-drugs.
Humankind	Guideline	014	011	We would recommend that clearer guidelines are provided for the minimum options for withdrawal that should be available for each drug, regardless of location or stage of treatment, and a clear outline of what patients are entitled to, including psycho-social options.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to

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					the existing dose, and for gabapentinoids by a fixed amount each time. Recommendations are included to consider providing details of sources of peer support, national and local support groups and helplines for people who are withdrawing from a medicine, and there was also evidence to recommend considering group cognitive behavioural therapy (CBT) to support people to manage symptoms when withdrawing from a benzodiazepine. There was insufficient evidence for interventions to support withdrawal from other medicines or for other interventions, but research recommendations have been included on this.
Humankind	Guideline	015	005	It would be helpful to include drug-by-drug specific detail in this section. If it is not feasible to provide more detailed guidelines, we would recommend the guidance signpost to other resources such as https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse and https://www.benzo.org.uk/manual/ and the RCGP Factsheets: https://www.sldtraining.co.uk/courses/resources	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the

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					recommendations do describe a schedule that guides dose reduction but enables flexibility in approach. NICE guidelines follow methodology set out in the NICE guidelines manual. If other guidance is incorporated it must meet the same methodological criteria as set out in the methods manual, and the protocols relevant to the review question.
Humankind	Guideline	018	002	We would recommend that research is also carried out into the gaps of care that exist within the system, especially the gap caused by commissioning that often leads to a disconnect between prescribing and delivery; such research would enable us to better understand the size of the issue.	Thank you for your comment. This was not a specific review question that was considered in the guideline and therefore a research recommendation has not been included in the guideline.
International Institute for Psychiatric Drug Withdrawal	Guideline	015	011-012	As written, this guidance (1.5.10) is potentially inaccurate and not supported by scientific evidence. There is no pharmacological reason to differentiate gabapentinoids from the other drug classes to order to recommend tapering by fixed dose reduction. The hyperbolic relationship between dose and effect on target receptors has not been demonstrated, as for the other 4 drug types, because PET scanning has not been performed for gabapentinoids. However, the relationship between dose and effect is hyperbolic for all pharmacological agents due to	Thank you for your comment. This recommendation was formed by committee experience and knowledge of PHE and NHS reports on safe use of gabapentinoids, as well as the summary of product characteristics (SPC) guidance on tapering. These all recommend reducing by fixed amounts. In the committees experience most schedules are slower than the manufacturers recommendations in the SPC to minimise withdrawal and re-emergence of symptoms. The references provided have been checked for inclusion in the guideline evidence review, however, neither are relevant to include. Delahoy et al. 2010 is in a population excluded

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				the law of mass action (Holford, 2018). There are no drugs evincing a linear relationship of dose and effect. Due to the law of mass action, whereby as more molecules of a drug are present, receptors are increasingly saturated, so each additional milligram of drug has incrementally less effect.	from the scope of this guideline (use of gabapentinoids for epilepsy) and also reports sensitivity and specificity data which is not relevant to the review protocol for safe withdrawal. Holford 2018 is an opinion piece / narrative review and so is not a relevant study design.

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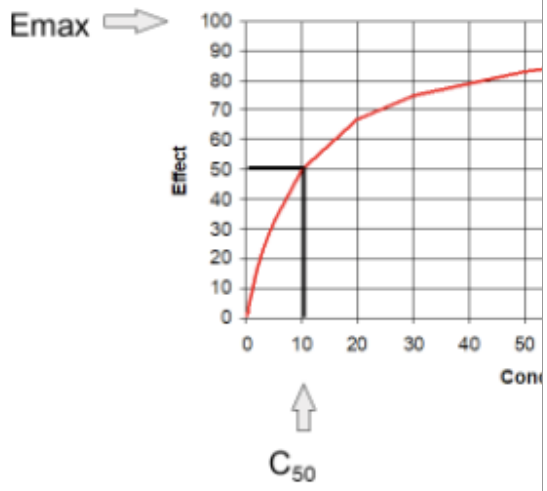
				This yields a hyperbolic plot:  Figure 2. Concentration, effect and the Emax The typical hyperbolic pattern is sometimes obscured by plotting dose response curves on a logarithmised x-axis, making the curve into a sigmoid shape that appears linear for intermediate doses, giving the false impression of linear dose-response effects:	

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				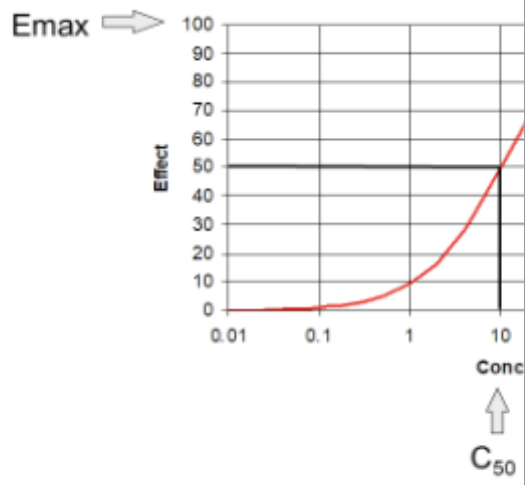 Figure 3. Log Concentration and Effect. (Diagrams from Holford 2019) Indeed, in Delahoy, et al., 2010, there is clear evidence of a hyperbolic relationship between dose and clinical effect for gabapentinoids. Using data from Table 4 in this paper which shows the relationship between dose of pregabalin and gabapentin and the mean	

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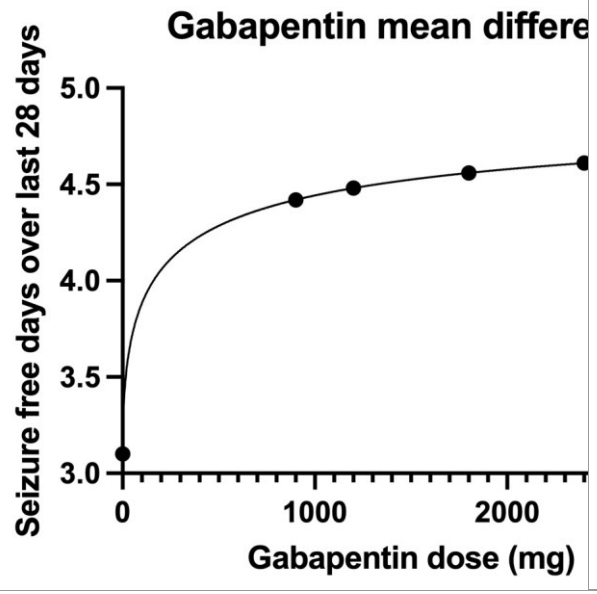
				number of seizure free days in a month form a typical hyperbolic relationship between dose and effect. Although this is a specific clinical effect (i.e. on seizures) this is likely to be representative of other effects (including withdrawal symptoms) because of the law of mass action determining the relationship between dose and effect.  	

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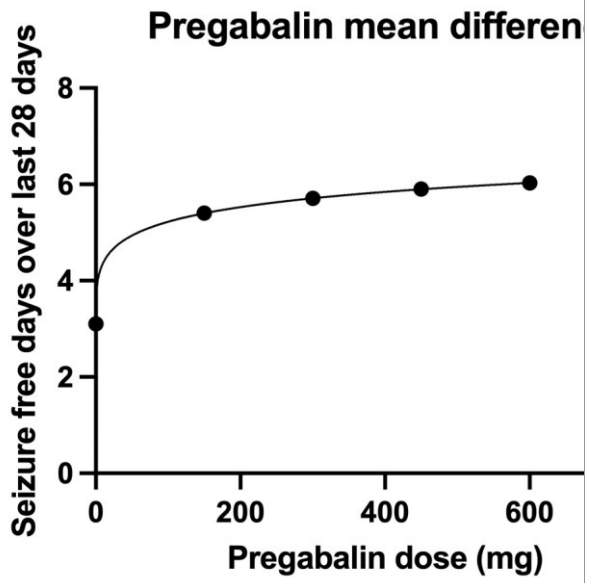
				The relationship between dose of gabapentin and seizure free days out of 28 days (derived from Table 4 in Delahoy et al, 2010). Placebo (graphed as 0mg of gabapentin) causes 3.1 seizure free days.  The relationship between dose of pregabalin and seizure free days out of 28 days (derived from Table 4 in Delahoy et al, 2010). Placebo	

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				(graphed as 0mg of gabapentin) causes 3.1 seizure free days. NICE's default position should be to taper drugs hyperbolically due to the law of mass action; it would require an extraordinary rationale to suggest linear tapering. This guidance should be revised to specify hyperbolic tapering (or the proportionate tapering that is a reasonable approximation to hyperbolic tapering) for gabapentinoids, as with the other psychotropics. Delahoy, P., Thompson, S. & Marschner, I.C. Pregabalin versus gabapentin in partial epilepsy: a meta-analysis of dose-response relationships. BMC Neurol 10, 104 (2010). https://doi.org/10.1186/1471-2377-10-104 Holford, N. (2018) 'Pharmacodynamic principles and the time course of delayed and cumulative drug effects', Translational and Clinical Pharmacology, 26(2), p. 56. doi: 10.12793/tcp.2018.26.2.56.	
International Institute for Psychiatric	Guideline	019	002-005	We are concerned about the research recommendation (4) focus on "Individual circumstances and the risk of dependence", which mistakenly looks for sociological or psychological triggers for the inevitable biological process leading to physiological dependence.	Thank you for your comment. This research recommendation has been reworded to look at the risk of problems associated with dependence, rather than the development of dependence. The references you have provided have also been checked for inclusion in the guideline evidence reviews however, we

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Drug Withdrawal				This research recommendation is premised on a misunderstanding of physiological dependence, a physiological process not related to social circumstances, distress, or co-morbid condition, but a predictable, homeostatic neurobiological response to drugs that alter neurotransmitter levels for sustained periods (Hyman and Nestler, 1996; Lerner and Klein, 2019; O'Brien, 2011; O'Brien, 2018). The implication throughout this document that there are sociologically defined groups at higher risk of physiological dependence erroneously conflates physiological dependence with the psychological drivers associated with addiction. This misdirects clinicians' and researchers' attention away from the effect of long-term drug use on neural (and other) tissue and the important question of how to safely discontinue drugs of dependence. The fact is, all people prescribed drugs of dependence and taking them regularly will adapt to the psychotropics and develop physiological dependence (Hyman and Nestler, 1996; Lerner and Klein, 2019). We urge the committee to make the sense of this research recommendation consistent with their own definition of dependence in the Context section. As written, this research aim	note they were included for information relevant to points made and are therefore descriptive articles/literature reviews, which do not meet the review protocols.

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				will distract people and resources from the necessity to research optimal clinical use, prescription, and safe discontinuation of drugs of dependence instead. Hyman, S. E. and Nestler, E. J. (1996) 'Initiation and Adaptation : A paradigm for Understanding Psychotropic Drug Action', (February), pp. 151–162. doi: 10.1007/s00340-005-2128-3. Lerner, A. and Klein, M. (2019) 'Dependence, withdrawal and rebound of CNS drugs: an update and regulatory considerations for new drugs development', Brain Communications, (2019). doi: 10.1093/braincomms/fcz025. O'Brien, C. (2011) 'Addiction and dependence in DSM-V', Addiction (Abingdon, England). 2010/10/06, 106(5), pp. 866–867. doi: 10.1111/j.1360-0443.2010.03144.x. O'Brien, C. P. (2018). Chapter 24: Drug Use Disorders and Addiction. In L. L. Brunton, R. Hilal-Dandan, & B. C. Knollmann (Eds.), Goodman & Gilman's The pharmacological basis of therapeutics. (13th ed.). McGraw-Hill Medical.	

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MIND	Guideline	General	General	Mind welcomes this guideline. We know that withdrawing from prescribed drugs can be difficult, and that people often struggle to get the right support and advice when coming off medication. It is also crucial that people are given clear information and support when they are making decisions about taking prescribed drugs. We welcome the guideline's emphasis on proper support and advice so that people can make informed decisions about their care.	Thank you for your comment.
MIND	Guideline	General	General	We recognise that antipsychotic drugs from this guideline scope and we urge consideration is given to further guidance on that class of drugs.	Thank you for your comment. The medicine classes to be included were agreed during the scoping process for this guideline. It was agreed that medicines such as antispsychotics are outside the remit of this guideline due to the requirement for specialist management. Guidance on their safe prescribing is included within the NICE guideline for psychosis and schizophrenia in adults CG178.
MIND	Guideline	004	020	We suggest that advocates and advocacy services should be added to the list of sources of support during appointments.	Thank you for your comment. This has been added to the recommendation as suggested.
MIND	Guideline	006	001	Medication decisions can also be difficult for people with a history of addiction, lack trust in medical services/healthcare professionals, or who aren't comfortable with medication (for	Thank you for your comment. The committee acknowledge this is not the only circumstance in which decisions may be difficult, however, it is one in the committee's experience can be overlooked in this context. History of drug misuse is included as one factor to consider when considering taking a

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				personal, religious, or cultural reasons). We suggest adding these at this point.	medicine. Recommendation 1.2.3 also cross-refers to the NICE guideline on shared decision making to support people when making decision.
MIND	Guideline	006	003	It may be worth stating that, if you are delaying prescribing until after the first appointment, to make sure a follow up is booked then and there (where possible) so that the individual is more likely to return to discuss options. Someone with depression and/or anxiety might find it difficult to make a follow up appointment on their own initiative. Additionally, we suggest strengthening this point to state that 'wherever possible, allow time for....'	Thank you for your comment. The recommendation has been reworded to include a statement that a follow up appointment should be arranged. The wording of this recommendation is 'consider' implying this will not always be the case, but is an option for the prescriber should it be necessary.
MIND	Guideline	006	018	At Mind we know that the lived experience is important, especially in this area where much learning and practice development has been in response to the lived experience of patients and their knowledge of taking and coming off prescribed drugs. We suggest that it important that people making decisions about whether to take a prescribed drug, or when and how to withdraw from a prescribed drug should have access to high quality independent information, such as that provided by mental health charities, e.g., see Mind's information resources on	Thank you for your comment. The committee consider that charities and resources they provide are adequately covered by the term 'sources of peer support and local or national support groups'.

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				stopping and coming off medication and psychiatric medicine. We suggest adding an additional line to the 'Information and support for people starting a medicine' section: 'Consider supplementing verbal and written information with details of online or written resources from other organisations (such as charities) who provide independent information on taking prescribed medicines.'	
MIND	Guideline	006	020	We suggest adding 'written information in an accessible format', such as easy read document, email/text, large text document.	Thank you for your comment. 'In their preferred format' has been added to this recommendation.
MIND	Guideline	007 011	005 014	As well as pregnant women, there are also additional implications for individuals taking hormonal treatments (such as for menopause, contraception or as part of transitioning). Particularly if the individual is experiencing depression (as these hormonal treatments can also impact mood). These should also be considered.	Thank you for your comment. The committee acknowledge that there will be other groups of people or comorbidities that require consideration when starting or reviewing medicines. The examples stated here are not intended to be all inclusive. These recommendations should be applied alongside condition-specific guidance and clinical judgement.

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MIND	Guideline	007	015	We suggest specifying that with antidepressants, individuals may feel worse for a short period of time.	Thank you for your comment. This is addressed in recommendation 1.3.3 which states that there may be a delay before benefits are experienced and side effects may be experienced before any benefit.
MIND	Guideline	007	020	The information included in the plan should also include what to do if you forget to take a dose.	Thank you for your comment. An additional bullet point has been included in the recommendation of information that should be given to the person before starting treatment, that missing doses may lead to symptoms of withdrawal. However, the committee considered that detail about missing doses and how to take the medicine applied to all medicines, not just those associated with dependence and withdrawal covered in this guideline and was also covered in the NICE guidelines on Medicines adherence and Medicines optimisation which are cross-referred to in the section for reviewing medicines.
MIND	Guideline	008 010 011 015 017	016 016 009 018 014	The parameters for what are considered"regula" or"frequen" for reviews should be considered. These are very subjective terms. There are many individuals on antidepressants who are not given any reviews at all or are told to arrange it themselves which, as outlined above (page 006, line 003), can be very difficult for those of us with anxiety and depression. It may not be feasible to have a strict timeline for all people, but recommendations on perhaps a minimum time period to give a baseline would	Thank you for your comment. The committee considered that the necessary frequency of review would vary between people, depending on their personal circumstances as well as the drug they were withdrawing from. They made a recommendation to state that regular intervals for reviewing the reduction schedule should be agreed, and also that frequency of reviews may need to be increased particularly during dose adjustment. The committee agreed that providing a minimum time period may risk people being seen no more frequently than this. A recommendation was included to highlight particular situations that might require more urgent review, and cross-

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				be beneficial (such as at least monthly for the first 3 months, then every 3 months following that).	references are provided in this section to the NICE guideline on depression where there are also considerations for review of antidepressant treatment.
MIND	Guideline	009	001	We suggest adding another paragraph to the 'Working with other healthcare professionals' section to emphasise the importance of working with other healthcare professionals when necessary: 'Healthcare professionals should consult with others in cases where the health professional's experience and expertise are limited, or where the patient's withdrawal is difficult'.	Thank you for your comment. The recommendations should be applied alongside the healthcare professional's clinical judgement. The committee consider that good practice would always be for a healthcare professional to consult with colleagues if they to do not have the relevant expertise and that is not specific to this guideline. However, a recommendation has been added to section 1.2 to ensure that prescribers have the time and support to make decisions about prescribing medicines, including to consult with colleagues where needed.
MIND	Guideline	011	028	We suggest rewording this to say, 'the benefits and disadvantages the person is experiencing from continuing the medicine', which would make the statement inclusive of side effects they may be experiencing.	Thank you for your comment. This bullet has been reworded to include both the benefits and harms.
MIND	Guideline	012	015	Again, it would be more balanced to state 'benefits and disadvantages' the person can expect from reducing the medicine, rather than just 'benefits'.	Thank you for your comment. This recommendation is intended to be about discussing the benefits of withdrawal when continuing the medicine is no longer in the person's best interests. The committee considered that people are often anxious about stopping their medicine and information about the benefits they will achieve by doing so is helpful at this stage. The recommendations in this section do go on to

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					include what people should expect when withdrawing from the medicine including possibility of withdrawal symptoms and how difficult this may be,
MIND	Guideline	014	015	We suggest adding 'online forums' to the list of sources of support here.	Thank you for your comment. The committee consider that online forums are adequately covered by the term 'sources of peer support'.
MIND	Guideline	014	017	We suggest adding an additional bullet point here: 'Consider supplementing information with details of online or written resources from other organisations (such as charities) who provide independent information on withdrawing from prescribed medicines.'	Thank you for your comment. The committee consider that charities and resources they provide are adequately covered by the term 'sources of peer support and local or national support groups'.
MIND	Guideline	014	017	As well as recommending possible sources of support, establishing what existing support and options an individual has for day-to-day activities during this time would be relevant here. For example, side effects from withdrawal may briefly impact ability to go to work or do essential tasks and a person may need practical support here. We suggest adding another bullet point: 'Consideration should be given to the practical support needed should side effects impact on a	Thank you for your comment. The committee agree and acknowledge that withdrawal can be a difficult process. The view of the committee is that recommendations for a slow withdrawal schedule that is tailored to the individual needs of the person and includes flexibility to adapt as required, can help minimise the problems experienced. There was very little evidence to inform other interventions to support withdrawal however, research recommendations have been included on this topic.

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				person's ability to carry out day to day essential tasks or go to work'.	
MIND	Guideline	014	021	We know that withdrawal can be a long process for some people, that it can persist for months or longer and is not a standardised process. We welcome the advice that clinicians should explain to patients that 'withdrawal can be difficult and may take several months or more'.	Thank you for your comment.
MIND	Guideline	015	005	Given our concerns at Mind about the need for appropriate support and guidance to be available to patients when they are withdrawing from medication, we suggest inclusion of more detail for clinicians about withdrawal symptoms in the section on 'Dose reduction'. In addition, consideration should be given to providing more detail on tapering, how to introduce smaller doses and the intervals between dose reductions.	Thank you for your comment. The committee do not agree that example withdrawal symptoms should be included within the recommendations. This is because the evidence is very limited in quantity and quality, and the committee agreed that withdrawal symptoms could vary widely between individuals in terms of which symptoms were experienced, but also in terms of intensity and duration. Providing a list of symptoms within the guideline could have a negative effect, leading to symptoms being overlooked if not on the list, or wrongly implying these symptoms if new did not require any further investigation. This has now been detailed in the rationale for that section. The committee agreed it was important to highlight the variability in withdrawal symptoms, and to talk to people about what they might expect. They agree it is important to highlight that it can be difficult to distinguish withdrawal

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					symptoms from recurrence of the condition, and had reflected that in a recommendation which also included examples that would help distinguish these in line with your comment. The guideline also recommends this is discussed with the person so that they are aware and contact a healthcare professional as necessary. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that guides dose reduction but enables flexibility in approach, and does not imply that dose reduction always has to follow a predefined trajectory, as that may not always be the most clinically appropriate approach for the person.

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MIND	Guideline	015	014	We suggest this should be reworded so that instead of 'consider', this should be 'wherever possible'.	Thank you for your comment. 'Consider' is used to in part denote the level of evidence and strength of the recommendation. In this case the evidence was not strong enough to recommend that this should be offered to all people, and so is worded as 'consider'.
MIND	Guideline	015	028	We suggest adding another paragraph to the 'Identifying and managing withdrawal symptoms' section to emphasise the importance of working with other healthcare professionals when necessary: 'Healthcare professionals should consult with others in cases where the health professional's experience and expertise are limited, or where the patient's withdrawal is difficult. This may include consultation throughout all stages of the withdrawal process with psychological therapists with expertise in withdrawal.'	Thank you for your comment. The recommendations should be applied alongside the healthcare professional's clinical judgement. The committee consider that good practice would always be for a healthcare professional to consult with colleagues if they to do not have the relevant expertise and that is not specific to this guideline. However, a recommendation has been added to section 1.2 to ensure that prescribers have the time and support to make decisions about prescribing medicines, including to consult with colleagues where needed.
Multiple Sclerosis Trust	Guideline	General	General	The MS Trust welcomes the development of this guideline. A number of symptomatic treatments for people with multiple sclerosis, for example gabapentin and pregabalin, are associated with dependence and withdrawal symptoms. It is vital that people being offered one of these treatments have a clear understanding of the benefits and risks of starting the medication, and fully understand the	Thank you for your comment. The committee agree, and have made recommendations on the information and support people should be given when considering these medicines including the information highlighted in your comment. The recommendation states that this should be provided as both written and verbal information.

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				importance of adherence and the need for gradual reduction of the dose when stopping treatment. As well as verbal information about the treatment, it is important that written information is also provided.	
NHSE and Improvement	Guideline	General	General	Overall this is an excellent piece of much needed guidance – thankyou	Thank you for your comment.
NHSE and Improvement	Guideline	007	009	May I suggest that it would be important to include antidepressants in the list of drugs – clinicians should be discussing the potential risks of dependence etc – omission of antidepressants may have the unintended consequence of suggesting that there is no risk of dependence – and/or that tolerance may occur – Taking the opportunity to explain the likelihood (or not) of these problems with antidepressants is important.	Thank you for your comment. The committee do not agree that antidepressants should be included in the list of drugs where risk of dependence is discussed. As stated in the context for this guideline, and in the scope, antidepressants are historically not classified as dependence-forming medicines, although they can nevertheless cause withdrawal symptoms when they are stopped. This is consistent with other reports on this topic, for example the Public Health England Prescribed Medicines Review published in 2019.
NHSE and Improvement	Guideline	007	017	I agree – this is helpful… but would also suggest inclusion of advice about the potential for wrong/misleading information to be found on some online forums. Acknowledgement that Some people are likely to search for information that supports their pre-conceived view may be helpful.	Thank you for your comment. The committee agree this is possible, and have therefore worded this recommendation as 'consider providing' and also state that it should be suitable for the person, implying the healthcare professional need only pass on information of services they consider appropriate for the person. Whilst the committee agree that wrong/misleading information can be found online, this has

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					not been included in the recommendation specifically as it was thought this may appear to be conflicting guidance.
NHSE and Improvement	Guideline	007	019	Advice on safe storage should also be included – particularly if there is likely to be anyone in the household felt to be at risk of intentional- or unintentional self harm.	Thank you for your comment. This has now been included in the recommendation for information that should be given to people when they start taking medicines.
NHSE and Improvement	Guideline	007	019	People who may initially present with symptoms that require treatment with antidepressants/benzodiazepines may be in distress & have reduced ability to focus/understand the management plan – I suggest scope is built into to guidance to allow for the information to be repeated at future visits.	Thank you for your comment. The committee agree that people may not be able to focus or take in the information at the time of the appointment. They recommended that information is given in both verbal and a written format that the person can take away to read later for that reason. They agree that the information in the management plan should be repeated and updated at future visits, and a copy again given to the person. This is recommended in recommendation 1.4.6 for review consultations.
NHSE and Improvement	Guideline	008	025	regarding quantity/storage – Advice on safe storage should also be included – particularly if there is likely to be anyone in the household felt to be at risk of intentional- or unintentional self harm would also be relevant here	Thank you for your comment. Advice on safe storage of controlled drugs is included within the NICE guideline for controlled drugs, which this recommendation cross-references to. A separate consideration has also been added to the recommendation of what information should be given to the person when starting treatment (1.3.1) to include information on safe storage of the medicine.
NHSE and Impro	Guideline	009	039	This recommendation requires further work… The importance of individualising treatment with these drugs cannot be underestimated. On the	Thank you for your comment. These recommendations have been reworded. All other recommendations in the guideline still apply to the healthcare professional in this context, and

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vement				other hand it is important to maintain treatment in line with best practice guidance (which I assume is the intention of this recommendation?)	therefore further considerations about best practice have not been added here specifically.
NHSE and Improvement	Guideline	012	001	…or the views of those close to the patient	Thank you for your comment. The committee do acknowledge that the views of people close to the patient may be helpful to inform a decision on whether to stop or reduce use of a medicine. However, the committee are mindful of ensuring recommendations reflect best practice in shared decision making, and that decisions are made with the person's consent and have therefore not stated this here. The recommendations for supporting people also include asking people whether they would like to have support during appointments from a family member, carer or other person close to them. This applies throughout and would be of relevance when making decisions to withdraw from medicines.
NHSE and Improvement	Guideline	012	030	It would be usual practice to continue antidepressant treatment for up to 6 months even though the acute symptoms may have responded earlier– therefore a slight rewording of this recommendation may be helpful eg • the condition for which the medicine was prescribed has resolved and the treatment is no longer needed to reduce the risk of premature relapse.	Thank you for your comment. The recommendations should be interpreted using the healthcare professional's clinical expertise and alongside other condition specific NICE guidelines. These points are intended as reasons you would consider discussing withdrawal, not necessarily reasons to definitely withdraw, and therefore the committee consider they are appropriate across medicines as written.

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NHSE and Improvement	Guideline	014	003	Also important to take account of long/short half life of benzodiazepine and also whether or not the active metabolites have long/short half lives (eg fluoxetine/desmethylfluoxetine)	Thank you for your comment. This recommendation provides some examples that might influence risk of problems during withdrawal, but is not intended to cover everything. A later recommendation highlights that for benzodiazepines if the person is withdrawing one with a short half-life to consider switching to one with a longer half-life.
NHSE and Improvement	Guideline	014	013	Suggest add - or medicines (in order to take account of complexities of multiple medicine use)	Thank you for your comment. The committee agree that this may apply to withdrawal of more than one medicine however, this has not been added to the recommendation as it is considered as written it does not rule out the option that more than one medicine is being withdrawn.
NHSE and Improvement	Guideline	014	018	Suggest also make reference to withdrawal symptoms emerging days/weeks after medication has stopped e.g diazepam	Thank you for your comment. A statement has been added to this recommendation highlighting that symptoms can vary in timing and may persist over a prolonged period.
NHSE and Improvement	Guideline	015	022	Suggest some additional guidance is needed here eg Consider switch to an **equivalent dose** of benzodiazepine with a longer half life for gradual taper	Thank you for your comment. The recommendation as written does not preclude starting at an equivalent dose. However, as this section is about dose reduction the committee considered you might switch to a lower dose and therefore have not amended the wording.
NHSE and Improvement	Guideline	016	030	This needs re phrasing to take account of the recommendation to consider switch to longer half life benzodiazepine	Thank you for your comment however, we are afraid we are unclear what this point relates to and therefore are unable to provide a specific response.

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NHSE and Improvement	Guideline	017	006	Change cannot – to should not … clearly the drugs "can" be abruptly stopped …but this should not normally be done	Thank you for your comment. This has been changed as suggested.
NHSE and Improvement	Guideline	020	006	If this research recommendation is included in the final guideline, I suggest re-wording the recommendation p15 line 22	Thank you for your comment. The committee acknowledge that more research is required to inform other options to support dose reduction and manage withdrawal symptoms, however, the line in the recommendation you refer to, does cross-reference relevant sections in the guideline where the current options with evidence are recommended. It is intended that if more research on these topics is carried out, it might be possible to recommend more options here.
NHSE and Improvement	Question 1	General	General	It will be essential to ensure equity of implementation across all medicines/patients – Whilst the individual strategies to manage /treat/ prevent to development of dependence may vary – health systems must ensure that strategies are in place to manage all the medicines subject to this guideline – and for example should not seek to exclude a particular group of medicines from being reviewed	Thank you for your comment. The committee agrees that there are areas that may need support and investment, such as training costs, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines. We have passed your comment to the NICE implementation support team to inform their support activities for this guideline.

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NHSE and Improvement	Question 2 and question 3	General	General	Consideration to include all groups of medicines likely to cause dependence as a priority for an initial structured medication reviews /triage review by PCN clinical pharmacists	Thank you for your comment. The committee agrees that there are areas that may need support and investment, such as training costs, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines. We have passed your comment to the NICE implementation support team to inform their support activities for this guideline.
NHSE and Improvement	question 4	General	General	There are already substantial pressures facing both primary and secondary care services – it will be important to frame the guideline in a way that does not generate a knee jerk response to refer everyone back to their G.P – or secondary care specialist. Implementation of the guidance should highlight the importance of preventing "new" cohorts of patients who become dependent on the drugs. There will need to be a phased approach to implementation/management with early work to identify those patients who are able to reduce/withdraw with minimal additional support – and also those who will require significant	Thank you for your comment. The committee agrees that there are areas that may need support and investment, such as training costs, to implement some recommendations in the guideline. However, this will ensure that the prescribing of medicines associated with dependence and withdrawal symptoms is safe and helps ensure the best care for people who are prescribed these medicines. We have passed your comment to the NICE implementation support team to inform their support activities for this guideline

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				additional support with possible multiple agency involvement… and also the group who may require a moderate degree of support – perhaps highlighting the need for a triage approach?	
NICE GP forum	Guideline	General	General	This guidance is an important opportunity to provide a strong steer and support prescribers who are trying to tackle very high dose prescribing.	Thank you for your comment.
NICE GP forum	Guideline	General	General	This guidance is, however, drafted along the medical model – most substance misuse training/teaching does not follow this model of care and incorporates more holistic features	Thank you for your comment. The committee note that the remit of this guideline is on safe prescribing of medicines associated with dependence and withdrawal symptoms, not substance misuse more generally. They agree that a holistic approach is important, and believe that the focus of the recommendations does reflect this by highlighting the need for an individualised approach considering the persons circumstances and preferences and considering all treatment options. The recommendations reiterate throughout that decisions making should be shared between the person and the healthcare professional. The guideline does however start assuming that non-pharmacological options have been discussed and offered where appropriate, as stated on the overview page for the guideline, and in recommendation 1.2.1. From there on the guideline does focus on situations relating to the prescribing process as per the remit of the guideline.

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NICE GP forum	Guideline	General	General	The majority of our respondents commented that there is no mention of the potential for diversion (ie patients selling/giving some/all of their medication supply for profit or to friends/ relatives). There are risks for the individual and the wider community. It may also be overlooked in non-community care settings.	Thank you for your comment. The remit of the guideline was safe prescribing of medicines associated with dependence and withdrawal symptoms. Illicit use was outside of the scope of this guideline and therefore specific mention of diversion of medicines has not been included.
NICE GP forum	Guideline	004	016	The need for stronger advice for continuity of care was mentioned by the majority of our respondents. The advice should also be specific to this guideline rather than hyperlinking to CG 138.	Thank you for your comment. In development of this guideline it was agreed that there are sections of CG138 that are of particular relevance to the safe prescribing guideline, and therefore it was thought important to highlight these sections rather than duplicating information that is already available in other NICE guidelines.
NICE GP forum	Guideline	004	016	Please add suggestions on how to promote/ support continuity. Where dependence and withdrawal is an issue, people benefit from continuity of care and a trusting understanding relationship. Without a proactive approach to follow-up patients get lost in the system NB. patients rarely contact Drs for reduction.	Thank you for your comment. The committee do agree continuity of care and fostering a trusting supportive relationship is important. This is reflected in recommendation 1.1.1. Additionally, as this is covered within NICE guideline CG138 it was agreed that this should be cross-referenced rather than duplicating information. Recommendation 1.3.14 also states that if possible, 1 person should have overall responsibility for a prescription, but if not, should ensure arrangements for review and effective communication are in place.
NICE GP forum	Guideline	005	003	A majority of respondents asked for joint planning/ MDTs where patients are being looked after in primary and secondary care to reduce	Thank you for your comment. The committee agree that joint planning is important. Recommendations reflect the need for effective communication between healthcare professionals. The recommendations on working with healthcare

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				the risk of dependency, and also to reduce conflict. Please add a note to consider any OTC medications the patient may be taking, including low dose opiates	professionals have been edited further to clarify this following stakeholder comments. The committee agree that over the counter medicines the person is taking should be considered, but note that this should be part of the general discussion of management options and understanding the persons circumstances.
NICE GP forum	Guideline	005	007	The majority of our respondents pointed out that alcohol misuse past or present was not mentioned here	Thank you for your comment. This has now been added to recommendation 1.2.2 where the evidence was for history of substance misuse, including both drug and alcohol misuse.
NICE GP forum	Guideline	005	015	Please clarify this. Our understanding is that short-acting opiates increase addiction due to the 'hit' and that conversion to long acting is appropriate when tailing down doses.	Thank you for your comment. The recommendation to avoid using modified release opioids was informed by the evidence review of risk factors associated with dependence. It is acknowledged that the evidence had limitations, however the committee agreed that it was from a relatively large cohort and was consistent with their clinical experience. The committee do not agree that immediate release, or standard release alone is riskier. In their experience, people on standard release opioid regimens tend to use lower average opioid doses (and are therefore exposed to fewer harms) than those on fixed dose modified release regimens. The recommendation has been moved to the prescribing strategies section, and edited to clarify that this is one possible step that can be considered to minimise risk of problems associated with dependence, reflecting both the strength of the evidence and the fact that it might not be

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					appropriate for everyone. The rationale for this recommendation now states this unless clinical considerations or the persons circumstances dictate otherwise. Recommendations to perform a benefit-harm assessment and to make a shared decision with the person still apply.
NICE GP forum	Guideline	009	001	Please include guidance to support joint planning /MDT approaches. This may include previous attempts to deprescribe	Thank you for your comment. The committee agree that joint planning is important. Recommendations reflect the need for effective communication between healthcare professionals. The recommendations on working with healthcare professionals have been edited further to clarify this following stakeholder comments and include noting that the healthcare professional should ensure that they have sufficient knowledge of the person's health and preferences, which would include previous attempts to deprescribe.
NICE GP forum	Guideline	009	001	Prescriptions may also be initiated elsewhere e.g. out of hours or by private providers. Please add guidance that the GP is notified so that monitoring of prescriptions can take place.	Thank you for your comment. The recommendations on working with other healthcare professionals are intended to cover taking over a person's care from any other healthcare professional. It is outside of the remit for NICE guidelines to make recommendations for private prescribers unless they are providing NHS commissioned services.
NICE GP forum	Guideline	010	001	Please change 'while discussions continue' to 'while the issues are resolved' and include a comment that patients shouldn't end up as the go-between. Please add recognition that refusal is very stressful for everyone involved.	Thank you for your comment. This recommendation has been reworded considering stakeholder comments.

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NICE GP forum	Guideline	010	011	Pharmacy staff (eg clerks as well as pharmacists) may raise concerns through recognising inappropriate requests.	Thank you for your comment. The committee noted there may be a number of people involved, and therefore use the terms 'prescribers' and 'healthcare professionals' so as not to specify any particular profession in the majority of cases. If concerns are raised by another member of the team, the committee agree these should also be considered, however it is not possible to specify all eventualities in the recommendations.
NICE GP forum	Guideline	010	016	Please also highlight patients with a high 'centrally acting load" for an holistic review I.e. those on two or more of these medications	Thank you for your comment. The committee noted that there are other reasons that may indicate the need for more frequent review. Those stated here are examples of reasons that may be particularly relevant for medicines associated with dependence and withdrawal symptoms. The committee consider that people taking two or more of these medicines would also fall under the consideration of 'potential for adverse effects and problems associated with dependence' and so have not added this as an additional reason.
NICE GP forum	Guideline	011	009	…and support them to navigate follow-up appointment systems	Thank you for your comment. This has been not been added to the recommendation as this was not part of the evidence reviews so practical guidance on navigating follow-up appointment systems cannot be included.
NICE GP forum	Guideline	011	012	Please add an extra bullet point: " when there are concerns about misuse or overuse"	Thank you for your comment. The committee do agree that this is a factor that merits more regular review, however the factors included in these bullets are things that the person will be able to identify themselves. The recommendation above (1.4.1) includes this as a factor that might indicate a need for more frequent reviews (potential for problems associated with

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					dependence). Recommendation 1.4.5 includes any signs the person is developing problems with dependence as a factor that would help inform the decision to continue or stop a medicine, as something that will be ascertained as part of the review.
NICE GP forum	Guideline	011	021	Please add a bullet point: "Assess/Calculate Total daily opioid load from acutes and repeats issued e.g. over the last 3 months"	Thank you for your comment. The committee note that there are other factors that should be considered as part of a medicines review. Those stated within this review are examples of those specific to those that would inform the shared decision to continue or stop. Further guidance on medication reviews is included in the NICE guideline for medicines optimisation which is cross-referenced to from this guideline.
NICE GP forum	Guideline	012	005	At what morphine daily equivalent dose should reduction be seriously considered? eg 120mg for non-malignant pain (https://www.nice.org.uk/advice/ktt21/resources/medicines-optimisation-in-chronic-pain-pdf-58758008162245) It is important to state this.	Thank you for your comment. The evidence reviewed within this guideline did not inform a specific morphine daily equivalent dose at which you would consider dose reduction. The committee agreed this would vary according to the individual based on a balance of risks and benefits. However, they did agree it was important to note that doses should not be automatically increased if the response is not sustained and have added this in recommendation 1.3.8.
NICE GP forum	Guideline	012	008	This is an important consideration as it may be complicating the picture of over-ordering or suspected addiction.	Thank you for your comment. The committee agrees that this is an important point to include.

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NICE GP forum	Guideline	013	001	Specific guidance here would be invaluable. What should we tell patients about the risks of prolonged opioid use (other than dependence) e.g.endocrine side-effects?	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that a healthcare professional can follow but enables flexibility in approach. The remit of this guideline was safe prescribing of medicines associated with dependence and withdrawal symptoms, and so the recommendations focus on issues relating to these factors rather than other side effects relating to the medicines. It is noted these recommendations should be applied alongside other condition specific guidance and other resources about the medicines.
NICE GP forum	Guideline	013	008	It would really help the prescriber if more detail is given, specifically naming higher risk medicines (especially anti-depressants)	Thank you for your comment. The medicines included in the guidelines were considered by class. Where evidence suggested a specific consideration for a medicine, this was separated out in the recommendation. However each of

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					these classes were considered equally important to consider in terms of their potential for causing problems associated with dependence.
NICE GP forum	Guideline	015	006	There was a unanimous request from our respondents for more detailed guidance in this section A barrier to dose reduction is knowing what is likely to work. For opioids (the commonest): - consider calculating morphine daily equivalent dose - avoid co-prescription of short and long-acting preparations where possible - consider a starting dose reduction of x% adjusted according to shared decisions. Drug specific guidance for reducing the other named medication groups would be very useful.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that the recommendations do describe a schedule that a healthcare professional can follow but enables flexibility in approach.
NICE GP forum	Guideline	015	006	There is no advice for people on multiple drugs, often a mix of street illicits and prescribed medicines. The evidence suggests that reducing one drug/agent at a time whilst maintaining stability with the others has better patient outcomes.	Thank you for your comment. The evidence reviewed did not inform specific recommendations for people with concomitant illicit drug use, and management of this was outside of the remit of this guideline. An evidence review was also not included to address priorities of medicine reduction if more than one was being tapered. The committee's view is that it is not always appropriate to follow a scientific rationale for which medicine should be reduced first without considering the person's individual circumstances and preferences. As

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					well as this the decision would depend on the individual circumstances and the balance of benefits and harms, including signs that the person was developing problems with dependence relevant to the medicines the person was taking.
NICE GP forum	Guideline	015	006	Please acknowledge possible timescales to dissuade commissioners from settling arbitrary time limits. Reductions for polydrug use can take many months to several years.	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. A recommendation is included highlighting that withdrawal can be difficult and may take several months or more (recommendation 1.5.9).
NICE GP forum	Guideline	016	020	We welcome the references to CBT and acupuncture, but these appear understated when the evidence points to the importance of psychosocial interventions. These can also be wider ranging and include support with housing, finances etc. Other complementary therapies also have some evidence of benefit in the holistic management for these patients	Thank you for your comment. The recommendation for CBT when withdrawing from a benzodiazepine was based on evidence and a cost-effectiveness model. Recommendations are also included to consider providing details of sources of peer support, national and local support groups and helplines for people who are withdrawing from a medicine. There was insufficient evidence for interventions to support withdrawal from other medicines or for other interventions, but research recommendations have been included on this, including the research recommendation for acupuncture. As well as this there is also a research recommendation for psychological interventions to support withdrawal, and a research recommendation for the most effective service model to support withdrawal, and research recommendations for

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					withdrawal from gabapentinoids, and other aids to support withdrawal.
Nottingham and Nottinghamshire CCG	Guideline	General	General	Antidepressants are different to the other medicines in this guidance. It is not usual that a clinician is faced with a patient requesting increasing doses of the antidepressant. Are issues pertaining to withdrawal of antidepressants better dealt with in the NICE guidance for depression and anxiety and not in this guidance?	Thank you for your comment. It was agreed during scoping that antidepressants would be included within this guideline due to the associated problems related to withdrawal from these medicines. This is also consistent with the Public Health England review on prescribed medicines. In many cases the committee agreed the evidence informed recommendations for general principles that applied to all medicine classes within the guideline scope. Where separate recommendations were required for a particular class (or classes) of medicine, these have been separated out within the guideline.
Nottingham and Nottinghamshire CCG	Guideline	General	General	The context in which opioids, gabapentinoids and benzodiazepines are prescribed is very different. The issues related to problematic use of these medicines and withdrawal from these medicines are also very different. I wondered if these could be presented as individual sections, like the way they are presented in the evidence summaries. There can then be reference to guidance related to safe prescribing individual medicines, risks of developing tolerance, potential for problematic use, planning dose reductions, withdrawal symptoms, strategies for managing withdrawals, strategies for managing	Thank you for your comment. The class specific recommendations have now been separated out from the general principles that apply to all medicine classes within scope.

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				the original condition that the medicine is prescribed for etc.	
Nottingham and Nottinghamshire CCG	Guideline	005	007-014	Reading this paragraph, I fear that patients with a comorbid mental health diagnosis or history of substance misuse might be excluded from appropriate treatment. The equality impact assessment states that "the committee highlighted in the rationale and discussion of the evidence that these should not be barriers to prescribing, and a shared decision on the use of medicines should be based on full consideration of the balance of risks and benefits." Should this be made explicit in the recommendation? Does "not having a clear, defined diagnosis to support the prescription" belong in these bullet points? If there is not a defined diagnosis, there is not an indication for a prescription?	Thank you for your comment. The fact that these should not be a barrier to prescribing has been added to the recommendation as suggested. The statement on lack of a clearly defined diagnosis arose from the evidence reviewed, highlighting that some people with painful conditions are prescribed medicines rather than other treatment options which can be more likely to lead to problems associated with dependence. This is detailed in the rationale and discussed in more detail in evidence review E.
Nottingham and Nottinghamshire CCG	Guideline	012	019-023	The guidance states that there is considerable debate in relation to these definitions of dependence and addiction and that the terms are often used interchangeably. This paragraph states that practitioners should be sensitive to terminology that may be perceived adversely. It is not clear how terms such as dependence or addiction will be perceived by patients, they can often be disempowering. I wonder if there might	Thank you for your comment. The committee agree discussions on sensitive issues can be challenging. However, providing recommendations on how healthcare professionals should communicate is beyond the scope of this guideline and applies to a range of topics. Other NICE guidelines such as the shared decision making guideline also make recommendations relevant to this and should also be followed.

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				be a section on how best to communicate such sensitive issues with the patient and the language that is found to be supportive. There might be focus on problems related to the use of medicines exploring the patient experience and working with the patient to identify motivation for change.	
Pain Concern	Guideline	General	General	Overall the guideline is well constructed and very person centred. The qualitative review is a good addition.	Thank you for your comment.
Pain Concern	Guideline	General	General	There is no mention of the importance of having structures in place in primary care to support deprescribing eg a practice policy, template - it would be helpful for research to be done on what system interventions in primary care would support this being done safely eg Wigan CCG have produced excellent resources on this . It's not just an implementation issue – the GDG should think carefully about what should be done now to support practices rather than making research recommendations.	Thank you for your comment. The guideline evidence review for withdrawal interventions was intended to be broad to identify evidence for any intervention to support withdrawal, however no evidence was identified for practice policy templates or similar,. The committee did make a research recommendation of relevance about the most effective service models in supporting withdrawal from medicines associated with dependence and withdrawal symptoms. Recommendations are based on the best available evidence, therefore when evidence is lacking in an area and recommendations are not considered appropriate to form from committee experience, research recommendations are made to inform future updates of the guideline.
Pain Concern	Guideline	General	General	The review is very generic and it is clear that there is very little research available that describes how best to withdraw opioids and	Thank you for your comment. The guideline does include recommendations to inform general principles to guide safe reduction of the medicines considered, including opioids and

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				gabapentinoids . This means that patients, who fear their medicines being deprescribed without support are left with no guidance on what they should look for	gabapentinoids. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They make recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time. The committee therefore consider that recommendations do guide dose reduction, but enable flexibility in approach. The committee agreed that a key factor was the rate of reduction of any of the medicines included in the guideline should be acceptable for the person, and there should be regular review and flexibility in the schedule to adapt this as needed. This is all reflected in the recommendations.
Pain Concern	Guideline	General	General	There is little guidance on when to involve a substance misuse service in deprescribing when should substitution therapy be considered Hall NY, Le L, Majmudar I, Mihalopoulos C. Barriers to accessing opioid substitution treatment for Opioid Use Disorder: A systematic review from the client perspective. Drug and alcohol dependence. 2021 Feb 26:108651.	Thank you for your comment. The committee considered that the recommendations in this guideline would enable safe withdrawal from the medicines in all NHS settings where these medicines are prescribed and therefore did not refer specifically to substance misuse services. The committee agreed that for the medicines included within this guideline, substitution with another medicine associated with dependence did not help withdrawal and could lead to harms,

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					and therefore, they recommended against this. The reference you have provided has been checked for inclusion in the guideline evidence review, however, the objective of the systematic review does not match that of the guideline review and so it is not relevant to include and would not alter the recommendations for substitution therapy.
Pain Concern	Guideline	General	General	There is little acknowledgement of the fact that PTSD is significantly associated with high opioid use, instead only CBT is mentioned. This means that little of the correct safety netting will be done Dahlby L, Kerr T. PTSD and opioid use: implications for intervention and policy. Substance abuse treatment, prevention, and policy. 2020 Dec;15(1):1-4.	Thank you for your comment. The guideline included a review on risk factors that were associated with dependence or withdrawal symptoms with these medicines. The review identified that there was an increased risk of problems associated with dependence in people diagnosed with mental health disorders including post-traumatic stress disorder. They therefore made a recommendation to consider this (and other factors that were also associated with increased) when making prescribing decisions. However, they also noted that these factors alone should not be barriers to prescribing. This is detailed in the rationale and the discussion of the evidence in evidence review E. The reference you have provided has been checked for inclusion in the relevant review but given that it is a descriptive article rather than a primary study it did not match protocol inclusion criteria.

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RCPsych	Guideline	General	General	We welcome this draft guideline and its focus on supporting patients and clinicians with shared decision making. While we note that the draft guidance appropriately distinguishes between antidepressants and the other three drug groups covered in terms of not being dependence forming, College members have expressed concern that this nuance was not in the communications about the launch of the draft guidance. We ask that this be considered when the final guidance is published.	Thank you for your comment. This is included as a statement in the guideline context, which is published online with the guideline.
RCPsych	Guideline	06	20	When these are prescribed in hospital settings, and potentially in primary care, we suggest that the draft guidance recommends that information about the medicine is discussed verbally and that written information is offered (not necessarily always given).	Thank you for your comment. The committee believe that as well as verbally the information should also be given in a format that people can read later as sometimes people may want time to think things through, or they may not be able to take it in at the time of the consultation. The committee considered this can also apply to people in hospital.
RCPsych		07	10-12	As the guidance is relatively high level, it lacks details and support for how to explain concepts of dependence and tolerance to patients. These are complicated concepts, and the way they are explained can impact on what is taken away from a consultation and may have important implications for what treatment is chosen/continued or not. It would be helpful if the guidance, or supplementary information to	Thank you for your comment. Providing example explanations for patients is beyond the remit of the guideline, however, the text in the context of this guideline has been amended to better explain dependence and addiction, how the terms differ and how they are used in the guideline which can help inform discussions.

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				the guidance, provided some specific examples of what to say to patients to explain these terms.	
RCPsych	Guideline	15	13	We believe that the advice to 'ensure that the rate of reduction is likely to be tolerable for the person' is too ambiguous, does not sufficiently reflect the importance of slow tapering and does not provide enough support for patients and clinicians. While we note that there is insufficient evidence to provide a guide tapering rate, and each individual will be different, it is important to provide clearer information in this area. The College's patient information resource, Stopping antidepressants, provides example tapering regimens which provide a guide and, importantly, demonstrate how slowly tapering should be for some people. We encourage the Committee to consider how it can reflect the need to provide some guidance on slow tapering for antidepressants for those individuals who need it.	Thank you for your comment. The recommendations for dose reduction are not limited to the one you highlight. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time.An additional recommendation has been added to acknowledge use of published withdrawal schedules but notes that if used these should be applied flexibly.
Royal College of General Practi	Guidance	009	018	The RCGP feels this recommendation needs to be made even clearer. Secondary care clinicians can prescribe for their own patients either on hospital out patient scripts or on FP10s long term if they wish to. It should not be expected by secondary care clinicians that further prescriptions will be provided of potentially	Thank you for your comment. The committee agree this is important to make clear in the recommendations. The recommendations have been reworded to strengthen this, using your suggested rewording as a basis for the edits.

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tioners				dependency forming medications in primary care, and patients should always be made aware of this risk when transferring medication responsibilities. We would like to suggest the following wording to strengthen the recommendation "explain to the person that any further prescriptions of the medicine are the responsibility of the primary care prescriber, who will review the need to continue the medicine *and if they do not agree, may not continue to prescribe the medication. In this instance, the prescribing responsibility should continue to lie with the secondary care clinician until a resolution is found."* It is very common for patients to be told they will receive a prescription from primary care e.g benzodiazepines , and when primary care teams do not agree to prescribe them to receive patient complaints. Adding in the additional wording, will ensure patient expectations are clear and enable GPs to refer the patients back to secondary care, who can either offer an alternative, or if they feel the mediation is required, arrange a timely conversation with primary care or continue the prescription directly with the patient.	

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Royal College of General Practitioners	Guidance	010	001	This recommendation as it is written risks significant delays in patient prescriptions and could be detrimental to patient care and the patient doctor relationship. We would recommend the wording as above, (*In this instance, the prescribing responsibility should continue to lie with the secondary care clinician until a resolution is found.")* so that until a decision is made that the prescribing responsibility should stay with secondary care aiming to prevent any interruption in prescribing and to minimise the unintended patient consequences of waiting for communication between primary and secondary care.	Thank you for your comment. The wording of this recommendation has been amended along the lines of your suggested wording.
Royal Pharmaceutical Society	Guideline	General	General	The guidelines mention 'slow tapering' but we feel that this is open to too much interpretation and could be harmful. The guidance should include information on tapering rates, the interval between dose reductions, how to reduce doses and the overall duration of taper. The guideline appears to focus on quick withdrawal based on other incentivising factors such as SMART goals and this is not appropriate for this category of medicines. We believe that the patient should be empowered to be in control of the speed of tapering	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They made recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to

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					the existing dose and for gabapentinoids by a fixed amount each time. The committee do not agree that the guideline focus on quick withdrawal, the recommendations (as stated above) highlight the opposite, that this should be slow. Recommendations also highlight the need to monitor and consider the person's individual circumstances and ensure this rate of reduction remain tolerable for them, as well as noting that withdrawal can take several months or more. The committee agreed that a key factor was the rate of reduction of any of the medicines included in the guideline should be acceptable for the person, and there should be regular review and flexibility in the schedule to adapt this as needed. This is all reflected in the recommendations. The committee also agree that empowering the person to control their dose reduction is important and can be helpful for some people. A statement was included in the recommendation for dose reduction to consider giving individuals additional control over the process of dose reduction, to reflect this.
Royal Pharmaceutical	Guideline	General	General	There is no real mention throughout about the importance of communication with all those involved in the patients care e.g. community pharmacists important particularly where abuse	Thank you for your comment. The committee agree that community pharmacists may play an important role. Where the recommendations refer to the person involved in the patient's care, the term 'prescriber' or 'healthcare

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Society				is a factor, leading to for example over-ordering which sometimes gets missed by prescribers. This can not only facilitate early intervention in the case of issues that arise but can also prevent the patient from having to repeat aspects of their conditions or circumstances they may not want to. This should be with patients consent and may not be necessary in every case.	professional' has been used so as to encompass all relevant roles, including community pharmacists. Recommendation 1.3.14 also recognises that pharmacists working in primary care may play a key role in supporting prescribing. This would include community pharmacists.
Royal Pharmaceutical Society	Guideline	General	General	There are gaps in the guidelines around the withdrawal aspect which should include practical steps that professionals need to support patients • Tapering – including duration of taper • Dose reduction – including how to reduce medicines	Thank you for your comment. The evidence reviewed for dose reduction was limited. The committee noted that the appropriate reduction schedule would vary not only by drug class, but also drug within that class as well as the person's circumstances. They therefore agreed that specific details on rate and time between reductions (for example) should not be recommended as flexibility was key. They made recommendations to guide the general principles of safe dose reduction. Recommendations are also included for opioids, benzodiazepines, Z-drugs and antidepressants suggesting a slow, stepwise rate of reduction proportionate to the existing dose, and for gabapentinoids by a fixed amount each time.

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					The committee therefore consider that recommendations do guide dose reduction, but enable flexibility in approach. The committee agreed that a key factor was the rate of reduction of any of the medicines included in the guideline should be acceptable for the person, and there should be regular review and flexibility in the schedule to adapt this as needed. This is all reflected in the recommendations.
Royal Pharmaceutical Society	Guideline	006	003	We are concerned this recommendation could lead to patients' appropriate treatment being delayed unnecessarily due to hesitation on the part of the prescriber.	Thank you for your comment. The recommendation has been reworded to include a statement that a follow up appointment should be arranged so that it is clear that this will not be an indefinite delay. The wording of this recommendation is 'consider' implying this will not always be the case, but is an option for the prescriber should it be necessary. The delay is intended to only be short, as described in the rationale for the recommendation, and is intended to be used to ensure safe prescribing and avoid inappropriate prescribing due to pressure at the time of the appointment, or indeed to allow the patient themselves time to consider options.
Royal Pharmaceutical Society	Guideline	009	021 - 028	In these two recommendations it should be explicitly clear who has to create the management plan. It suggests here that the HCP in secondary care will do it but if the management plan contains some of the information it suggests from line 20 onward on page 7 it may not be appropriate for that HCP to undertake this prior to the HCP in primary care reviewing particularly if they have to start the	Thank you for your comment. The committee consider that the management plan should be created by the prescriber initiating the prescription (in a shared decision with the person), but that this should be transferring to anyone involved in ongoing prescribing or care of the person. This is stated in recommendation 1.3.13.

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				prescribing process. This could lead to confusion and duplicated work. This section needs to be reviewed and made clearer.	
Royal Pharmaceutical Society	Guideline	012	008	There are times when you may need to withdraw the medication (perhaps slowly) to see if the condition has resolved e.g. z-drugs or if it believed that the medicine is no longer benefiting the person, or if ongoing benefit is unclear. It may not always be clear the issue has gone away, and it is important to discuss this and encourage the patient to try.	Thank you for your comment. The committee agree and note that this recommendation does give other examples of when you might consider withdrawing the medicine, including if the harms of the medicine outweigh the benefits (amongst others).
Royal Pharmaceutical Society	Guideline	015	014	We do not believe this would work, the patient would just take their normal dose or at the first hint of a problem would be taking more than agreed. In practice, if you safety net appropriately, have an open discussion and the patient feels part of the discussion they should be able to come back to you if they are struggling.	Thank you for your comment. In the committee's experience this can work well for some people, as it empowers them to feel in control of the process rather than giving the impression it is being done to them and the medicine is being taken away. This is written as 'consider' because the committee agree it will not be appropriate for everyone.
Royal Pharmaceutical	Guideline	015	022	Also consider if on two or more benzodiazepines switching to an equivalent dose of one before reduction.	Thank you for your comment. The committee note that the recommendation as written does not rule out use in situations when two or more medicines are being used and therefore do not think this level of detail is required within the recommendation.

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Royal Pharmaceutical Society	Guideline	016	020	The guidance has a list of 'do nots' but does not provide any practical guidance on interventions. We would suggest that referring people to peer support groups (possibly online) should be included as well as the need for services including psych-social interventions.	Thank you for your comment. We agree this is important and have already included a recommendation (1.5.8) to consider providing details of peer support and support groups for people withdrawing from a medicine. The evidence for other interventions was insufficient to inform recommendations, but a number of research recommendations have been included on this topic to inform future updates of this guideline.
The Breastfeeding Network	Guideline	007	005-006	The guideline states: "Explain to the person…the additional implications of taking the medicine if the person is pregnant or planning pregnancy, if appropriate." The latest MBBRACE report released this year (Saving Lives, Improving Mothers' Care, Knight et al 2021, https://www.npeu.ox.ac.uk/mbrrace-uk/reports) gives a number of examples of failure to prescribe, or de-prescribing, medications such as antidepressants due to pregnancy unnecessarily and at serious detriment to the woman's own health. We suggest an addition to the guideline here that prescribers should refer to the UK Teratology Information Service (UKTIS, https://www.medicinesinpregnancy.org/) when discussing prescribing options with women who are pregnant or planning pregnancy, and ensure that they are adequately considering the	Thank you for your comment. This recommendation is intended to ensure people are given appropriate information when starting treatment, including any considerations if they are pregnant or planning pregnancy. This recommendation has been slightly reworded to state 'any additional implications' rather than 'the additional implications' to reflect that there might not be any relevant to the medicine they are taking. Breastfeeding has not been added specifically, as it is considered this would be part of the discussion with someone who is pregnant or planning pregnancy, if relevant to the medicine. The NICE guideline for Antenatal and postnatal mental health also includes recommendations for considerations relating to antidepressant use for someone considering breastfeeding.

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				needs of the woman, as well as the safety of the baby, rather than simply erring on the side of caution when prescribing. It should also be noted that that some drugs can cause poor neonatal adaptation as babies withdraw from placental transfer after birth, e.g. venlafaxine (https://www.ncbi.nlm.nih.gov/books/NBK501192/) , fluoxetine (https://www.ncbi.nlm.nih.gov/books/NBK501186/) or opioids. In these cases, the neonates may require additional monitoring and additional support may be required to establish breastfeeding. This is not necessarily a reason not to prescribe these medications if they are required, but alternatives could be considered. This should be discussed with the mother and any additional support that may be required included in her care plan. Additional consideration should also be given to medications to aid withdrawal from substances of dependence such as methadone, buprenorphine and nicotine replacement therapy. Again, neonates may require additional monitoring, and women may require extra support in this difficult transitional period to avoid returning to their drugs of dependence.	

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				We would suggest that an additional point be included here covering "the additional implications of taking the medicine if the person is breastfeeding or planning to breastfeed, if appropriate." Many medications that are associated with dependence or withdrawal are in fact compatible with breastfeeding, but some may be preferable over others due to possible side effects in the breastfed infant, and this should be considered when making prescribing decisions. From contacts to our Drugs in Breastmilk service (DiBM, https://www.breastfeedingnetwork.org.uk/detailed-information/drugs-in-breastmilk), we know that many women are concerned about taking medications such as antidepressants whilst breastfeeding, or have been advised by healthcare professionals that these medications are not compatible with breastfeeding, even when this is not the case. It is essential that the risks and benefits of Taking a medication or not, to both the mother and child, are discussed, alongside the risks and benefits of breastfeeding or not, and that an informed choice is made. adWhilst it will be possible to take many medications whilst breastfeeding, the mother	

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				may require reassurance that this is safe, and advice on safety considerations for the baby, for example, not bed-sharing if their medication makes them drowsy or sleep more deeply, and being aware of side effects to be alert for in the baby. The British National Formulary and summary of product characteristics (SPC) for such medications frequently take an excessively conservative stance on prescribing to breastfeeding women. Reference to these alone could result in the woman not receiving necessary treatment, or discontinuing breastfeeding unnecessarily. We would therefore like to see the guideline emphasise the importance of protecting breastfeeding wherever possible whilst also ensuring the mother receives the care that she needs. The guideline should refer prescribers to the NHS Specialist pharmacy service UK Drugs in Lactation Advisory Service (UKDILAS, https://www.sps.nhs.uk/articles/ukdilas/), the Drugs in Lactation database (LactMed, https://www.ncbi.nlm.nih.gov/books/NBK501922/) and the Breastfeeding Network DiBM service for the most accurate information on prescribing to breastfeeding women, to allow fully informed, shared decision making.	

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The Breastfeeding Network	Guideline	011	014	The guideline states: "Offer extra, unscheduled reviews when needed, for example if the person…becomes pregnant or is planning pregnancy". We would like to highlight here, as stated in the MBBRACE report 2018 and reiterated in the latest 2021 edition that "Decisions on continuing, stopping or changing medication in pregnancy should be made only after careful review of the benefits and risks of doing so, to both mother and infant" (Saving Lives, Improving Mothers' Care, Knight et al. 2018, https://www.npeu.ox.ac.uk/mbrrace-uk/reports). The latest MBBRACE report (Saving Lives, Improving Mothers' Care, Knight et al, 2021) showed that some women are still being advised to discontinue medications such as antidepressants due to pregnancy unnecessarily and at serious detriment to their own health. We suggest an addition to the guideline here that prescribers should refer to the UK Teratology Information Service (UKTIS, https://www.medicinesinpregnancy.org/) when discussing prescribing options with women who are pregnant or planning pregnancy, and ensure that they are adequately considering the needs of the woman as well as the safety of the baby,	Thank you for your comment. The recommendation is intended to highlight when you may want to consider additional reviews, and an opportunity for the person to discuss their treatment, so as to ensure safe prescribing of these medicines. The committee agree that decisions on continuing, stopping or changing treatment should be made only after careful review of the benefits and risks of doing so. This is explained in the further recommendations including the content of the review, and making shared decisions about stopping or withdrawing the medicine. The committee noted your comment that this may be of particular importance to people who are pregnant or planning pregnancy, however the committee agreed this equally applies to all people taking these medicines, and therefore people who are pregnant have not been separated out in these recommendations. The evidence reviewed did not inform more detailed recommendations on drug specific issues for people who are pregnant or breastfeeding. The committee agree that the UK Teratology Information Service is an important resource, but they consider this should apply for prescribing of all medicines in women who are pregnant or planning pregnancy rather than being specific to this guideline and so have not included a cross reference here. The committee do not recommend that medicines should be used to aid withdrawal from the medicines considered within

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				rather than simply erring on the side of caution when prescribing. It should also be noted that that some drugs can cause poor neonatal adaptation as babies withdraw from placental transfer, e.g. venlafazine (https://www.ncbi.nlm.nih.gov/books/NBK501192/) , fluoxetine (https://www.ncbi.nlm.nih.gov/books/NBK501186/) and opioids. Additional support may be required to establish breastfeeding in these neonates. This is not necessarily a reason to discontinue these medications if they are required but it should be considered and discussed with the mother and included in her care plan. Additional consideration should also be given to medications to aid withdrawal from substances of dependence such as methadone, buprenorphine and nicotine replacement therapy. Again, neonates may require additional monitoring, and women may require extra support in this difficult transitional period to avoid returning to their drugs of dependence.	the scope of this guideline. Therefore, recommendations on the use of methadone, buprenorphine and nicotine replacement therapy in pregnancy, or for other people are not included other than to advise against their use to aid withdrawal for opioids, antidepressants, benzodiazepines, Z-drugs and gabapentinoids.

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				We further suggest the additional example "gives birth and/or initiates breastfeeding" be added. If the person had been taking a medication covered by this guideline before or during pregnancy, the dose may have been adjusted, or the medication stopped, due to pregnancy, and this may require review. The postnatal period is a time of particular vulnerability to mental health problems. The MBBRACE report (Knight et al, 2021) recommends, particularly for women with mental health conditions: "If psychotropic medication has been discontinued in advance of, or during, pregnancy, ensure women have an early postnatal review to determine whether they should recommence medication, carried out either by the GP or mental health service depending on the level of pre-existing mental health care." Furthermore, if a person intends to breastfeed, they may be concerned about the impact of the medication on their baby, and this may need to be discussed. It is essential that the risks and benefits of taking a medication or not, to both the mother and child, are discussed, alongside	

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				the risks and benefits of breastfeeding or not, and that an informed choice is made. Whilst it will be possible to continue many medications whilst breastfeeding, the mother may require reassurance that this is safe, and advice on safety considerations for the baby, for example, not bed-sharing if their medication makes them drowsy or sleep more deeply, and being aware of side effects to be alert for in the baby. If the current medication is not considered compatible with breastfeeding, an alternative may be available. The British National Formulary and summary of product characteristics (SPC) for such medications frequently take an unnecessarily conservative stance on prescribing to breastfeeding women. Reference to these alone could result in the woman not receiving necessary treatment, or discontinuing breastfeeding unnecessarily. We would therefore like to see the guideline emphasise the importance of protecting breastfeeding wherever possible whilst also ensuring the mother receives the care that she needs. The guideline should refer prescribers to the NHS Specialist pharmacy service UK Drugs in Lactation Advisory Service (UKDILAS,	

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				https://www.sps.nhs.uk/articles/ukdilas/), the Drugs in Lactation database (LactMed, https://www.ncbi.nlm.nih.gov/books/NBK501922/) and the Breastfeeding Network Drugs in Breastmilk service (DiBM, https://www.breastfeedingnetwork.org.uk/detailed-information/drugs-in-breastmilk) for the most accurate information on prescribing to breastfeeding women, to allow fully informed, shared decision making.	
The British Pain Society	Guideline	General	General	Thank you for the opportunity to comment on this draft. We are generally supportive of the principles outlined.	Thank you for your comment.
The British Pain Society	Guideline	005	015-018	It is not made clear that starting opioids is rarely helpful in chronic long term conditions especially chronic pain. There is considerable talk about how to start it and which preparations but no caution as to starting them at all. Most specialist pain physicians would not consider starting opioids for chronic pain. Primary care physicians would be advised to consider the benefits of starting opioids in non-cancer pain. Opioids have a greater place in management of acute pain and are rarely considered for chronic	Thank you for your comment. The efficacy of the drugs for different conditions is outside of the scope for this guideline. Recommendations for (or against) treatment are covered within the condition-specific NICE guidelines, for example the NICE chronic pain guideline, NG193.

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				pain. The recommendation should be reviewed to ensure it clarifies when opioids are recommended.	
The British Pain Society	Guideline	009	016-029	Sections 1.3.10 and 1.3.11 talks specifically about the interaction between primary and secondary care. It may be more appropriate to talk about specialist care rather than secondary care as there are an increasing number of specialist services based in primary care settings	Thank you for your comment. The committee discussed the wording of this recommendation and agreed that it should remain as secondary care as this is where their experience suggests there is most variation in continuity when transferring care.