Review decision of NICE’s technology appraisal guidance on esketamine nasal spray for treatment-resistant depression

NICE’s technology appraisal guidance on esketamine nasal spray for treatment-resistant depression (TA854) was published in December 2022.

# Decision

The evidence received did not support the need for an update of the existing recommendations.

So, the guidance will remain unchanged unless or until NICE becomes aware of new substantive information to support reconsideration. NICE will continue to monitor this topic for further evidence. It may also reconsider this decision if there are significant changes in the treatment pathway in the future (such as new treatments in the pathway).

# Rationale

The initial review proposal was that an update was not needed because the new evidence did not show a greater relative benefit compared with current treatments than that considered in TA854. This proposal was consulted on with stakeholders.

At consultation, stakeholders thought that the new evidence from ESCAPE‑TRD:

* provided additional certainty compared with a more relevant comparator for augmentation therapy that would be used in clinical practice
* resolved other clinical uncertainties such as the trial length.

NICE acknowledges that aspects of ESCAPE‑TRD reduce structural uncertainty by providing a more appropriate comparison of relative effect. But, the analysis presented to committee in TA854 had already included parameters for relative effect with a greater benefit than in the updated evidence. So, the committee had already considered scenarios including parameter values that showed greater benefit than the new evidence. So, new analysis and economic modelling is not needed to establish how this evidence would affect decision making. This is because the uncertainty resolved by the new evidence was not incorporated in the parameters underlying the cost-effectiveness calculations and associated uncertainty analysis in TA854.

At consultation, stakeholders noted that there is disparity in access to medicines for mental health and to medicines for physical conditions, which may be partly because of difficulties in evidence generation in mental health. The committee recognised the difficulties in designing, recruiting and interpreting results from clinical trials for mental health conditions. It took this into account in its decision making in TA854.

At consultation, stakeholders also raised further points to consider since the original appraisal of TA854, including evidence from other data sources and decisions made by regulatory bodies. Responses to these are available in the [consultation response form](https://www.nice.org.uk/guidance/ta854/history).

In conclusion, the new clinical evidence supports the current recommendation in TA854. New analysis is unlikely to result in a change to the recommendation at this time. In addition, there have been no changes to the marketing authorisation that would suggest the need for a further review, in line with NICE process.

# Summary of new evidence and implications for review

## Has there been any change to the price of the technology since the guidance was published?

The company had a confidential discount through a patient access scheme, which would have applied if the technology had been recommended. This has since been withdrawn, as per the NICE process. There have been no changes to the list price of esketamine nasal spray. If the technology had been reappraised, new commercial arrangements could have been considered.

## Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?

There have been no changes to the marketing authorisation for the technology for this indication.

## Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?

There was substantial uncertainty in the original guidance (TA854) about:

* treatment positioning and clinical pathway
* choice of comparator treatments
* internal and external validity of the clinical evidence
* long-term effects of treatment
* natural history of the condition
* resource use
* implementation.

The committee recognised that some of these uncertainties were common in evidence generated in many mental health conditions.

New results from ESCAPE‑TRD have been published in [Reif et al. (2023)](https://www.nejm.org/doi/full/10.1056/NEJMoa2304145). It concluded that esketamine nasal spray plus a selective serotonin reuptake inhibitor (SSRI) increases the proportion of patients in remission compared with quetiapine extended release (XR) plus an SSRI.

Quetiapine XR, positioned as a third-line or more treatment, is likely to be a more appropriate comparator than the oral antidepressants at second line or more that were considered in TA854. This is because quetiapine XR is an augmentation therapy, and esketamine nasal spray is likely to be used later in the treatment pathway (see [sections 3.3 to 3.5 of TA854](https://www.nice.org.uk/guidance/ta854/chapter/3-Committee-discussion#treatment-pathway-and-comparator)). So, this is a more relevant trial design for establishing the relative clinical benefit compared with currently available treatments. But this trial represents only 1 position of esketamine nasal spray in the treatment pathway, which compares it to newly starting augmentation therapy. So, some uncertainty would remain if the treatment was positioned in a highly heterogeneous and personalised pathway. The subgroup of people who have had 3 or more previous treatments was considered the most appropriate subgroup in TA854.

ESCAPE‑TRD’s primary outcome showed a rate of remission of 28.7% for the esketamine nasal spray arm compared with 18.2% for the quetiapine XR arm at 8 weeks. In TA854, the TRANSFORM‑2 trial was used as the main input into the economic model. As a comparison, it used the 4‑week remission rates considered by the committee for the 3 or more previous treatment-lines subgroup, which had substantially increased rates of remission. But, the company considered the numbers confidential, so they cannot be reported here.

ESCAPE‑TRD’s secondary outcome showed that the difference in Montgomery–Åsberg Depression Rating Scale (MADRS; a 60‑point scale with a score of 10 or less indicating clinical remission for the primary outcome) scores between the 2 treatment arms was 2.8 at 8 weeks and 2.2 at 32 weeks. Also, there was a mean least squares difference over the entire time period of 2.4. This was in the context of an overall reduction in MADRS score of about 20 points on the MADRS scale over the 32 weeks in the quetiapine XR arm. In TA854, at 4 weeks, the difference between arms was 4.0 for the full population covered by the marketing authorisation. In the 3 or more previous treatment-lines subgroup, the overall difference in MADRS was higher, but the value was considered confidential by the company so cannot be reported here.

For both outcomes, NICE recognises that this was a naive comparison, and that there were differences in trial designs and definition of remission. But, the comparison was appropriate for considering magnitude of effect size.

In TA854, the results of a network meta-analysis were considered unreliable because of heterogeneity in the available clinical evidence. So, an unadjusted analysis with trial results was used (see [section 3.6 of TA854](https://www.nice.org.uk/guidance/ta854/chapter/3-Committee-discussion#treatment-pathway-and-comparator)). Using a naive comparison of change in remission rates or change in MADRS score suggests that the benefit of esketamine nasal spray from ESCAPE‑TRD is smaller than the benefit of esketamine nasal spray considered by the committee in TA854. This new clinical evidence from ESCAPE‑TRD does not provide sufficient information to change the current recommendation.

Stakeholders highlighted that there are the higher levels of responses to all treatments in clinical trials compared with clinical practice. This is exacerbated in mental health conditions because of the difficulties of evidence generation. The committee also noted concerns about unblinding of treatment and how this may affect results. But, ESCAPE‑TRD was an open-label study, so results should be interpreted with caution.

The new evidence may provide some reduction in uncertainty about:

* treatment line (there is more evidence later in the pathway)
* comparator treatment (quetiapine XR is a relevant comparator)
* longer-term effects of the treatment (these results are for up to 32 weeks instead of 4 weeks).

But, it does not resolve many of the other substantial uncertainties with the evidence base or modelling concerns.

## Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?

[NICE’s terminated technology appraisal on esketamine for treating major depressive disorder in adults at imminent risk of suicide](https://www.nice.org.uk/guidance/ta899) is the only related piece of NICE guidance. This guidance has no implications for TA854.

# Equality issues

There were some potential equality issues raised in the original guidance:

* Geographical access may be an equalities consideration because an aspect of the condition is lack of energy and motivation. So, esketamine administration would need to be in the community setting. There were also concerns about equity of access in the criminal justice system. But, the committee considered that these issues were matters of equity, not equality, so would not be addressed.
* People who are underserved are more likely to have treatment-resistant depression.

# Decision paper sign off

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