NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Structural neuroimaging in first-episode psychosis

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Psychosis refers to severe symptoms of mental illness including the inability to distinguish between subjectivity and reality, with marked interference with the capacity to meet the demands of everyday life. Usually the person lacks insight into their condition. The term 'psychosis' describes a collection of symptoms but is not a diagnosis in itself. 'First-episode psychosis' refers to the first time a person presents with or experiences psychotic symptoms or psychotic episodes. However, it is often difficult to identify the precise time of onset. The current definition of 'first episode' could include people who have been treated for many years without remission as well as those who have had psychosis for only a short time and have not yet received treatment. A 2-year limit for the duration of a first episode of psychosis has been suggested, but this is not widely accepted.

Psychoses have been classified as being either functional or organic. Functional psychoses include schizophrenia and mood disorders such as

mania and bipolar disorder. Organic psychoses are those where the symptoms are associated with an identifiable physical illness such as encephalitis, a head injury or a structural lesion of the brain such as a tumour. The causes of psychosis vary by sex and age. Young adults who develop psychotic symptoms are most often diagnosed with functional psychosis, particularly schizophrenia. In contrast, most causes of psychosis in the elderly are organic. It is estimated that there is an organic cause of psychosis in 5–10% of people with the condition.

Organic psychoses are more likely to be of acute onset, and those associated with space-occupying lesions in the brain are likely to be accompanied by other neurological symptoms such as motor neurone paralysis, sensory loss, cranial nerve lesions and speech or hearing difficulties. Atypical psychosis refers to psychosis with unusual features, including psychoses of organic origin. In general, psychotic symptoms that are atypical would lead a clinician to suspect organic rather than functional causes of psychosis.

A person may suffer one or several episodes of psychosis before contact with healthcare services. The first point of contact is usually a healthcare professional, but other possible contacts include religious officials or faith healers, or workers in the criminal justice system. People with psychosis tend to have a poor quality of life (problems with carrying out daily activities and with social and sexual relationships). Quality of life tends to be lower where people with psychosis are single, or where they have psychiatric comorbidity, premorbid adjustments and behaviours, a long duration of psychotic symptoms, poor personal relationships and/or financial problems. Prognosis depends on the primary diagnosis.

There is some UK-specific information on the incidence of psychosis, but the most extensive information relates to schizophrenia or other functional psychoses rather than all psychoses. A Nottingham-based study examining the incidence of first-episode psychosis in two cohorts (1978–1980 and 1992–1994) found that the age-standardised incidence rate for schizophrenia and related disorders was 0.14 per 1000 per year. It was observed in this study

that the incidence rate for all psychoses was slightly (but not statistically significantly) higher in the later cohort, but the rate of schizophrenia was significantly lower. This might be due to the range of other diagnoses made in the later cohort.

The prevalence of psychosis appears to vary by ethnic origin. One study found a higher rate of functional psychosis in African, African–Caribbean and other black participants than in white people, while rates for South Asians were lower, after controlling for socio-demographic and other risk factors. However, these results could be due to chance.

Reported UK mortality rates related to psychosis for which schizophrenia was the underlying cause were 0.7 per million for men and 0.8 per million for women between 1996 and 2004. UK mortality figures for all psychoses are not available.

1.2 Current management

There is evidence that early intervention in first-episode psychosis improves symptoms and lowers relapse rates, and is effective in promoting functional recovery. In the UK, several initiatives (including National Service Frameworks) have been instituted with the aim of promoting specialist early intervention services for psychosis. In 2006, a National Early Intervention in Psychosis (EIP) programme was initiated with the aims of early detection of psychosis and reduced duration of untreated psychosis, with special emphasis on the first 3–5 years following onset, in order to achieve better long-term health outcomes. The programme includes research into the cost effectiveness of early intervention services for psychosis.

Clinical examination involves determining a history of the psychotic episode from the person and their relatives and friends. Standard physical, mental and neurological examinations and laboratory examinations are conducted to ascertain the possible underlying causes of psychosis. An encephalogram (EEG) may be conducted depending on the possible diagnoses. Indications that the underlying cause is organic are acute onset and features of delirium.

If an organic cause is suspected following standard clinical examination, confirmatory tests are carried out depending on the proposed diagnosis. These may include structural neuroimaging techniques, namely magnetic resonance imaging (MRI) and computed (axial) tomography (CT) scanning. If no organic cause is suspected following standard examinations, it is assumed that the person has functional psychosis.

There is a possibility that an organic cause may be missed in the group of people suspected to have functional psychosis. A CT or MRI scan may therefore be useful in identifying cases (misidentification syndromes) of psychosis where structural causes were missed in the initial examinations. Almost all people with psychosis are referred to psychiatric services unless they show symptoms and signs of other pathology, in which case they are sent to other medical specialties but are also given psychiatric advice.

Treatment depends on the cause of psychosis. Interventions for psychosis include both psychological therapies (family therapy and cognitive behavioural therapy) and pharmacological treatments (including conventional and atypical antipsychotics). Conventional antipsychotics include phenothiazines (for example, chlorpromazine and trifluoperazine) and butyrophenones (for example, haloperidol), and atypical antipsychotics include drugs such as olanzapine and risperidone. If symptoms are resistant to treatment (that is, the person has not responded to two antipsychotic medications from different classes given at adequate doses for sufficient periods, usually 6–8 weeks), the atypical drug clozapine may be used. Clozapine requires special monitoring to avoid serious side effects, including agranulocytosis, myocarditis and cardiomyopathy.

People with psychosis who are resistant to treatment should be distinguished from those who initially respond to treatment and then deteriorate. In the former group, MRI and CT scanning may be used to determine if an intracranial lesion is responsible for treatment resistance.

2 The technologies

Table 1 Summary description of technologies

	CT	MRI
Manufacturers	• GE Medical Systems • Phillips Medical Systems • Siemens Medical Solutions • Toshiba Medical Systems Ltd	• GE Medical Systems • Phillips Medical Systems • Siemens Medical Solutions • Toshiba Medical Systems Ltd
Acquisition cost (NHS reference costs 2005–2006)	£78 per scan	£244 per scan

Neuroimaging (also called brain imaging) is used for non-invasive visualisation of the anatomical structure and neuropsychological function of the brain. This appraisal covers the former (structural neuroimaging) but not the latter (functional neuroimaging). Structural neuroimaging techniques (MRI and CT scanning) assist in the diagnosis of intracranial pathology. A CT scan is a form of X-ray tomographic imaging where a series of X-rays are used to visualise two-dimensional slices through the body, which are recorded by a large array of sensitive detectors. MRI is also a tomographic imaging technique that exploits the nuclear magnetic resonance phenomena.

In order to perform a CT scan, the person must remain still. In addition, there are a number of systematic errors (artefacts) that can affect the quality of a CT scan. Consequently, CT scanning is not 100% sensitive or specific in the diagnosis of brain lesions. CT scans fail to detect lesions if they are of the same density as surrounding tissues. In this case, an iodine-based contrast dye may be used to help visualise these lesions. Contrast dyes are known to cause allergic reactions in some people. The main disadvantage of CT scans is the dose of radiation that is absorbed. It is estimated that 40% of all radiation absorbed by people as a result of diagnostic imaging is from CT scanning.

The main advantages of MRI in comparison with CT scanning are firstly that MRI does not involve the use of ionising radiation to generate images, and secondly that soft tissues can be clearly differentiated. In general, MRI is a safe diagnostic technique and few safety concerns are encountered in clinical practice. These safety concerns relate to interactions between magnetic objects (for example, pacemakers) and the MRI scanner, noise, hyperthermia, and peripheral nerve stimulation resulting in muscle twitching. The use of helium to cool the magnets may end up displacing oxygen and asphyxiating the person (however, this is a very rare occurrence). There is a refusal rate in the general public of approximately 5–10% because of anxiety and claustrophobia (this rate may be higher for people with psychosis).

The main disadvantage of MRI scanning is the number of false positive results. In a retrospective case series of 1000 healthy volunteers, 82% of MRI results were completely normal. Only 1.1% of people required urgent referral, and the remaining 16.9% had positive MRI results of no clinical significance.

MRI scanning provides higher image resolutions than CT scans and is the preferred option for most morphological investigations. It is most effective for images of soft tissues of the brain. A CT scan, however, provides the best images of bone and hard tissues. Whereas MRI can be used in pregnant women, CT scans are contraindicated because of ionising radiation. There are two main ways in which MRI can be used in the diagnosis of psychosis: visualisation of a region of interest where the radiologist focuses on the main parts of the brain that are thought to be different in people with schizophrenia, and an automated whole-brain analysis called voxel-based morphometry. A voxel is a three-dimensional volume element (see assessment report, page 17).

There have been a number of systematic reviews of region of interest visualisation, and studies to identify if certain structures of the brain are unique to schizophrenia. None of these systematic reviews identified any unique structures linked to the disease. However, a recent meta-analysis of studies of voxel-based morphometry indicated that structural defects in the

caudate nucleus, thalamus and white matter close to the uncinate fasciculus are plausibly linked with first-episode schizophrenia. However, these kinds of studies, although interesting from the point of view of investigating the aetiology of functional psychoses, are not directly relevant to this appraisal.

There is often a long waiting time for MRI (3–12 months) that undermines its usefulness for early intervention in the acute stages of psychosis. The waiting time for CT scans is shorter (2–4 weeks). There is very little routinely collected information on the use of structural CT and MRI scans for psychosis in the UK. In addition, studies on UK pathways of care do not often report investigations that are performed routinely. From NHS reference costs, approximately 70,000 CT and 57,600 MRI scans are carried out per year (but these are not specifically head scans). In old-age psychiatry, a greater proportion of people with psychosis are sent for a CT or MRI scan, possibly because the prevalence of organic causes of psychoses is higher in older people.

3 The evidence

No submissions were received from the manufacturers of the structural imaging equipment. The evidence base presented is that from the academic Assessment Group (AG). The decision problem for this appraisal is to determine whether it is clinically and cost effective to screen routinely all people with first-episode psychosis by either structural CT or MRI scanning, compared with standard clinical practice for the assessment of people presenting with first-episode psychosis.

3.1 Clinical effectiveness

The AG identified six CT studies, two MRI studies and one MRI/CT study that recruited people with first-episode psychosis. Other studies were identified that included populations at various stages of illness. The methodological quality of studies identified by the AG was, in general, poor, and classifying the study designs was difficult as the studies did not resemble conventional randomised controlled trials. The studies were more closely matched to

before/after study designs and mostly relied on retrospective data. There were no studies found that looked at the time to correct diagnosis or certainty of diagnosis. No studies were found in which people had specifically experienced deterioration in psychotic symptoms. The definition of first-episode psychosis varied from study to study, and the AG had to broaden its inclusion criteria for its literature searches and systematic reviews to cover more than just treatment-naïve people.

Quantitative meta-analysis of the results was not possible because of methodological heterogeneity, heterogeneity in populations, poor reporting of study outcomes, and sampling bias. The studies had varying proportions of psychotic diagnoses, and the service care and research settings differed, making it difficult to compare results between studies. Overall, the internal validity of the studies identified was questionable. No MRI studies and only two CT studies were conducted in the UK and this affects the external validity or generalisability of the results of studies identified to the general population and routine clinical practice in the UK.

Although a meta-analysis was not possible, the AG estimated from across the spread of results of the studies that MRI may identify lesions requiring a change in clinical management in approximately 5% of people with psychosis (range 0–10%). The corresponding figure for CT is approximately 0.5% (range 0–5%). There was only one, 'poor quality', study involving treatment-resistant/refractory schizophrenia and hence it was not possible to reach reliable conclusions about the effectiveness of CT and MRI scans in people with this condition. However, this study estimated that 2.2% of people with treatment-resistant/refractory schizophrenia had a scan that would affect the clinical management of the condition. The AG was not able to carry out subgroup analysis (by age or sex) because of a lack of reporting of relevant clinical outcomes.

The AG's review of case reports of misidentification syndromes also did not provide conclusive evidence. In the reports reviewed, 25% of the study population had scan results that influenced the course of clinical

management. The percentage of people for whom there was a change in diagnosis due to the scan was not reported. The most common cause of misidentification syndromes was schizophrenia, and hence extrapolation of these results to populations with organic psychosis is unclear and unreliable.

The AG's tentative conclusion is that structural neuroimaging in first-episode psychosis as a tool to be used in addition to standard clinical practice is not an effective method of detecting organic causes of psychoses. This conclusion is based on the results of studies that the AG considered to be generally poor, badly conducted and badly reported. High quality evidence of the benefit of CT or MRI for the diagnosis of people with psychosis was not found. A form of publication bias may have affected the retrieval of available research for judging the effectiveness of structural neuroimaging.

In view of the lack of evidence to support the use of structural neuroimaging in first-episode psychosis, the AG concluded that CT or MRI scans should only be used where there is uncertainty or poor medical history of the symptoms and signs of an organic cause of psychosis, or a space-occupying brain lesion, or where there is a positive past medical history. However, in the case of structural neuroimaging in psychosis, there is no single target condition being investigated. In general, when a CT or MRI scan is ordered, it is not known whether the person has a bony lesion that will be picked out better in a CT scan, or a soft-tissue lesion that is more likely to be found on MRI. This makes it inherently difficult to determine whether a CT or an MRI scan would be the more appropriate neuroimaging technique.

3.2 Cost effectiveness

3.2.1 Threshold analysis

The AG used a threshold analysis to estimate the cost effectiveness of routine structural neuroimaging in the diagnosis of a number of conditions associated with a first episode of psychosis, compared with the standard diagnostic strategy of selective scanning (that is, scanning only when medical history or physical findings suggest an increased likelihood of an organic cause of

psychosis). The framework of threshold analysis follows people for a period of 1 year. A 1-year time horizon and threshold analysis was developed as the most pragmatic means of evaluating the effectiveness of CT and MRI scanning. This was because of the paucity of data to populate an appropriate conventional decision-analytic model; for instance, data on differential responses to antipsychotic drugs depending on the (organic or functional) cause of psychosis, as well as data on the impact on quality of life of having an early rather than a late diagnosis of any structural cause of the psychosis.

The primary objective of the economic analysis was to evaluate the costs and health effects of MRI or CT scans only where structural causes of psychosis were not immediately obvious to the clinician, as the treatment pathway will be altered only in these cases.

The AG noted that some organic causes of psychosis, such as dementia or epilepsy, cannot be diagnosed using CT or MRI scans. Consequently, the diagnosis of only one organic cause was considered, namely brain tumours/cysts. The AG built a number of possible decision-analytic models; however, without the data to populate these models, a threshold analysis was considered the most appropriate for this appraisal. A threshold analysis is limited, however, as it doesn't consider the detailed progress of people through treatment pathways and the ensuing costs and consequences of routine scanning of a person's progress through the pathways.

The threshold analysis assumed that treatment of a brain tumour was not altered as a result of earlier detection with an MRI or CT scan. The analysis also assumed no deterioration in disease states when detected at a later stage with standard practice compared with early-stage detection with routine scanning. The cost of treatment for a brain tumour/cyst is common to both the routine and selective scanning strategies, as it was assumed that, even with the selective screening strategy, a diagnosis (and subsequent treatment) of a brain tumour/cyst would be achieved within a 12-month period. Incremental costs between routine and selective strategies were combined with the conventional acceptable threshold range of £20,000 to £30,000 per

quality-adjusted life year (QALY) gained in order to estimate the incremental QALY gain needed to make the routine strategy cost effective.

The incremental cost of routine versus selective scanning using MRI was directly affected by three uncertainties within the threshold analysis: (1) time period of treatment of the brain tumour, (2) antipsychotic drug dosage (a treatment strategy comprising consecutive use of three atypical antipsychotic drugs was assumed; see assessment report, pages 90–91), and (3) the relative proportions of people receiving hospital and home care during the monitoring phase. A scenario analysis was performed to explore these uncertainties.

The AG estimated test accuracy rates for detecting brain tumours/cysts to be 100% for MRI and above 90% for CT scans. The probability of detecting a brain tumour/cyst following an MRI scan in the relevant population was extracted from systematic reviews and estimated to be 5%. The probability of detecting a brain tumour/cyst with a CT scan was thus assumed to be 4.5% (with 0.5% false negatives). It was assumed in the base-case threshold analysis that CT scans had a 90% sensitivity rate.

Based on these assumptions, the strategy of routine scanning with MRI was found to be cost saving. The greatest cost saving was apparent when the largest proportion of people were hospitalised during the monitoring phase. A 50/50 split between hospital and home care had the biggest impact on incremental costs. Even with the conservative assumption that no people were hospitalised (0/100 split), routine structural neuroimaging was still cost saving.

Threshold analysis was carried out on the basis that, if QALY loss is greater than the cost saving at acceptable cost effectiveness threshold levels, then the technology is no longer cost effective. Hence as the cost savings from routine scanning become greater, so does the QALY loss needed to render MRI not cost effective. At a threshold value of £20,000 and under the conservative scenario of a 50/50 split in hospital/home care, a QALY loss of

0.011 for the full cohort and a QALY loss of 0.228 for people with brain tumours/cysts only is needed to offset cost savings. These QALY losses seem implausibly large, and thus routine scanning using MRI appears to be a cost-effective strategy (see assessment report, pages 93–94, for further details).

Similar threshold analyses were carried out by the AG for routine scanning using CT. The greatest cost saving scenario was that with the highest proportion of people receiving hospitalised care. When this proportion was zero, the antipsychotic drug dosage was low and the duration of treatment was 6 months, a routine scanning strategy was still cost saving. Threshold analysis suggests that QALY loss (needed to render routine CT scanning not cost effective) is greatest in the scenario where the proportion of hospitalised care is greatest, the dose of antipsychotics is highest, and the duration of treatment under selective screening is 12 months and that for people with false positives is also 12 months. Even with the conservative assumption of no hospitalised care, the required QALY loss appears implausibly high to render routine CT scanning not cost effective (see assessment report, pages 55–56).

In summary, threshold analysis for both MRI and CT showed that routine scanning was cost saving compared with selective scanning. These results were consistent across all scenarios in both cases. Cost savings are due mainly to the costs of antipsychotic medications and associated treatment costs following delayed diagnosis.

3.2.2 Sensitivity analyses

The AG carried out a number of sensitivity analyses. One major area of uncertainty investigated within the threshold analyses was the time period of inaccurate diagnosis under the selective scanning strategy. There was no information on the average length of time that a brain tumour/cyst is undetected. In the base-case analysis, a variable length of time (6–12 months) was assumed. This was changed to 3 months in the sensitivity

analysis. However, with a time delay of just 3 months before accurate diagnosis is achieved, routine scanning using both MRI and CT was cost saving.

It was assumed in the base-case threshold analysis that CT scans had a 90% sensitivity rate. This was varied to 50% (2.5% false negatives). Routine scanning using MRI or CT nonetheless remained cost saving under these assumptions.

The AG further conducted sensitivity analyses on the assumed prevalence of brain tumours/cysts in people with psychosis. The prevalence rate of brain tumours/cysts was varied to 0.5% and 1%. For MRI, routine scanning was no longer cost saving at these prevalence rates. Therefore, for MRI to be cost saving, a QALY gain would be needed. For all scenarios (duration of untreated psychosis, hospital and home care split, dose of antipsychotic treatments), the QALY gain needed to make MRI cost effective at a £30,000 per QALY threshold was small: 0.006 and 0.003 for the full cohort at 0.5% and 1% prevalence of brain tumours/cysts respectively.

The evidence for CT scans was mixed. When the prevalence rate of brain tumours/cysts was set at 0.5% and hospital care was given in fewer than 50% of cases, routine scanning was no longer cost saving and a QALY gain was needed to make CT cost effective at conventional thresholds. For all scenarios with a 50/50 split of hospital/home care, routine CT scanning was cost saving. When prevalence was set to 1%, routine CT scanning was cost saving under all scenarios.

Threshold analyses performed by the AG suggest that routine structural neuroimaging is cost saving, with potential savings for the population cohort ranging from £228 to £789 for MRI scanning and from £346 to £852 for CT scanning. The maximum acceptable QALY loss for MRI to be cost effective ranged from 0.011 to 0.039, and for CT the maximum acceptable QALY loss ranged from 0.017 to 0.043. These results appear robust to variations in the

various parameters investigated except for variations in prevalence rates of brain tumours/cysts in people with psychosis.

According to this analysis, whether routine MRI or CT scanning is cost effective appears to be influenced largely by quality of life (and QALY) gains or losses that result from scanning all people with psychosis. If routine scanning would not cause a QALY loss overall and the prevalence of organic psychosis due to a brain tumour/cyst lies in the region of 5%, then routine structural neuroimaging will be cost saving. Cost savings remain even if the delay in diagnosis of the brain tumour because of a selective scanning strategy is reduced to 3 months. If the prevalence of organic psychoses is close to 0.5%, then MRI is no longer cost saving, and CT is only cost saving if 50% of people receive hospital care.

3.2.3 Study limitations

The results of the threshold analyses, however, have to be treated with caution. Limitations of using a threshold analyses is its 12-month time horizon, and the failure to consider the detailed progress of people through different treatment pathways. In addition, it is assumed there is no deterioration in disease state resulting from late detection and diagnosis (selective scanning strategy), and that there are no mortality effects within the cohort. However, it is possible that quality of life (and QALY) gains from early detection by routine scanning may persist beyond 12 months.

There are a number of uncertainties surrounding the results of the threshold analysis. These include uncertainties about the prevalence rate of organic psychoses and model parameters estimated from poor-quality studies of the before/after type. Furthermore, quality of life (and QALY) losses might arise from radiation dose to the head from CT scanning and from missed pathology, as CT is not 100% sensitive. For MRI, quality of life (and QALY) losses may arise from noise and the claustrophobic nature of the investigation, and from incidental findings that might cause anxiety. In addition, treatment costs did not take account of the cost of subsequent treatment should another psychotic

disease develop following neuroimaging, or the cost of treatment following a false positive result.

4 Issues for consideration

Is there sufficient evidence on the usefulness of structural neuroimaging techniques in the routine clinical evaluation of people with first-episode psychosis?

Are there any subgroups of people with psychosis (for instance, by age and sex) in whom structural neuroimaging will be clinically and cost effective?

Does the threshold analysis provide sufficient economic evidence to make a decision on the technologies?

What is the impact of the uncertainties in the threshold analyses, in particular uncertainties relating to:

- treatment effectiveness estimates derived from poor-quality studies of the before/after type
- the prevalence rate of detectable structural causes of psychosis in UK populations of people with psychosis
- quality of life (and/or QALY) gains and losses associated with structural neuroimaging in first-episode psychosis?

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment Group, University of Birmingham.

- Albon, E., Tsourapas, A., Frew, E., et al. Structural neuroimaging in psychosis. Systematic review and economic evaluation; June 2007

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope and the assessment report. Organisations listed in I and II were also invited to make written submissions.

I Manufacturers/sponsors:

- GE Medical Systems
- Phillips Medical Systems

II Professional/specialist and patient/carer groups:

- Counsel and Care
- Rethink
- British Association for Psychopharmacology
- British Neuropsychiatry Association
- British Psychological Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Radiologists

III Commentator organisations (without the right of appeal):

- Department of Health , Social Services and Public Safety for Northern Ireland
- EUCOMED
- NHS Quality Improvement Scotland
- Institute of Psychiatry
- National Coordinating Centre for Health Technology Assessment

- West Midlands HTA Collaboration