Initiatives to shorten duration of untreated psychosis: systematic review

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Background
Long duration of untreated psychosis (DUP) is common and associated with poor outcomes. Strategies to enhance early detection of first-episode psychosis have been advocated.

Aims
To evaluate initiatives for early detection of psychosis.

Method
Systematic review of available evidence on the effectiveness of early detection initiatives to reduce the DUP.

Results
The review included 11 studies which evaluated 8 early detection initiatives. Evidence suggests that general practitioner education campaigns and dedicated early intervention services do not by themselves reduce DUP.

Conclusions
How early detection can be achieved is not clear. Evidence is most promising for intensive public awareness campaigns: these require organisation and resourcing at a regional or national level. More good-quality studies are needed to address gaps in knowledge.

Declaration of interest
None.

Long duration of untreated psychosis (DUP) is associated with poor outcomes for people with first-episode psychosis and poorer quality of life at first contact with services. Minimising DUP is a stated aim of early intervention services. However, long DUP is common: one systematic review found mean DUP of over 2 years; median DUP of up to 26 weeks has been reported. Treatment delays can occur both before and after someone has initiated help-seeking and made contact with health services. Strategies to reduce treatment delay for people with first-episode psychosis are widely advocated as a plausible way in which patient outcomes and experience of services may be enhanced. In the UK, guidelines from the National Institute for Health and Clinical Excellence (NICE) identify one defining responsibility of early intervention services as education of the wider community to reduce obstacles to early engagement in treatment. Aiming to reduce DUP by increasing the awareness of signs and symptoms of psychosis by professionals and/or the general public has been explicitly advocated by international experts and recommended for early intervention services in UK government guidance. The terms early detection and early intervention are used to describe both preventive interventions for people at risk of developing psychosis and interventions to provide prompt treatment for people once they have developed psychosis. This review is concerned only with interventions seeking to reduce treatment delay for people with psychosis. This is a comparatively uncontroversial and more commonly pursued aim for early intervention services, without the potential ethical and cost implications of providing treatment for people identified as at risk of subsequently developing psychosis.

A Cochrane review of early intervention for psychosis included early detection initiatives for people with first-episode psychosis. However, none of the available evidence was included, mainly owing to the inclusion criterion of randomised studies only. Three other reviews of early intervention include some studies of early detection initiatives. Only one of these, from 2001, reports a systematic search strategy and none describes and typifies different early detection approaches. In an expanding research field, an up-to-date, fully systematic review of all available evidence regarding early detection initiatives is therefore highly relevant.

Method

Inclusion criteria
Interventions
Studies of any intervention designed to enhance the identification and prompt treatment of people with first-episode psychosis were included. The review focused on interventions to reduce delays and facilitate access to treatment: studies evaluating the impact on patient outcomes of early intervention services once patients are in contact, or of specific treatment strategies, were therefore excluded.

Participants
The review included studies of interventions to promote identification and early access to treatment for people with first-episode psychosis. Studies concerning only populations at-risk mental states but yet to develop psychosis, or people already being treated for psychosis, were excluded.

Type of study
Any study comparing an early detection intervention with standard service procedures (in early intervention or other mental health services) was included. These included cluster randomised studies, two-group non-randomised comparison studies and historical comparison studies. Individual randomised controlled trials are not possible in studies of early detection initiatives as individuals cannot be randomly allocated to early detection strategies which, by their nature, target groups in the general population from whom referrals might be obtained.
Outcomes
Studies were included which evaluated any of the following outcomes:

(a) DUP of people with first-episode psychosis admitted to services
(b) number of people with first-episode psychosis admitted to services
(c) health status, experience of care or referral pathways of people with first-episode psychosis admitted to services
(d) the referral behaviour of groups targeted in early detection initiatives.

Search strategy
Four electronic searches were conducted, combining terms for psychosis and DUP or early detection, including filters for randomised controlled trials, observational studies, systematic reviews and grey literature. The searches were conducted across the following electronic databases from inception to May 2009: EMBASE, MEDLINE, PsycINFO, CINAHL and IBSS. Systematic reviews were additionally searched for in the Cochrane Database of Systematic Reviews and the Cochrane Database of Abstracts of Reviews of Effects (DARE) and randomised controlled trials were additionally searched for in the Cochrane Central Trials Register (CENTRAL). Grey literature was additionally searched for in HMIC and PsyCExtra databases. The search terms used in MEDLINE are provided on p. 4 of the online supplement to this article. Search terms were amended as required for searching other databases.

Grey literature was also sought using the free text and keyword searches of ZETOC, SIGLE, the National Health Service (NHS) National Research Register and UK Clinical Research Network databases. Reference lists from all included studies and relevant reviews were hand searched. Leading national and international research centres and services were contacted by letter or email to try to locate any unpublished data that might exist as a result of previous or ongoing evaluation.

All retrieved articles were imported and screened in Reference Manager. Duplicate articles were removed at the stage of whole article screening. Where studies were multiply reported, one main article was included in the review: where additional information was included in other papers, references were provided in the results section. The final inclusion total from the search thus represents the number of separate studies identified.

Selection of studies for inclusion in the review was made by a single reviewer (M.C. or B.L-E.). A subsample of 20 studies was assessed by a second reviewer (L.H.) to check adherence to inclusion criteria in study selection. Queries about inclusion were resolved through discussion with a third reviewer (S.J.).

Data abstraction
The following information was collected: study design, characteristics of the early detection intervention, stated outcomes, measures and results from the study.

Two domains were used to categorise early detection initiatives described in included studies: target group (whose behaviour the intervention was designed to influence) and medium of intervention. The primary target group was categorised as one or more of:

(a) mental health service providers
(b) other health professionals (e.g. general practitioners (GPs))
(c) workers in non-health community organisations (e.g. teachers, youth workers, faith group leaders, housing workers)
(d) a specific group of potential service users (e.g. school or college students)
(e) multifocus: more than one of the above groups or the general population.

The primary medium of intervention was categorised as one or more of: written or audio-visual information (printed material, television, radio, video, web-based); direct contact (individual or group education or training); or service configuration (changes in the organisation of mental health services such as the establishment of an early intervention service). Categorisation was undertaken separately by two reviewers (B.L-E. and L.H.); any disagreement was resolved by discussion or with reference to a third reviewer (S.J.).

Study quality was assessed using an assessment measure developed by Thomas.17 The measure allows studies to be rated as strong, moderate or weak in six key domains affecting study quality: selection bias, allocation bias, masking, confounders, data collection methods and withdrawals (before or during treatment). Criteria for assessing data collection methods were operationalised as follows: studies assessing DUP rated strong if DUP was defined and a published assessment tool was used in collecting DUP data; studies rated moderate if one of these criteria was met and weak if neither was met. For this review, no rating was made for two domains – masking and measurement of confounders. Given the public nature of early detection campaigns and the in-depth information about pathways through services required for DUP measurement, masking of participants or raters is not possible. The unit of comparison for early detection initiatives is areas (e.g. GP practice areas or regions) rather than individuals. There is no clear basis for deciding in advance which area characteristic should be measured. For studies of multifocus initiatives involving two or a few large areas, it is not evident how measured differences could be accounted for in analyses. For quality domains where ratings of quality were not made, relevant features of study design or recruitment were described.

Reporting of results
Results for all review outcomes were reported from all included studies. Mean and median DUP from studies are reported where possible. P-values are reported for all significant results from included studies. Assessment method and definition of DUP used by included studies are described in the data supplement. A narrative synthesis of included studies is presented.

Study selection
The literature search found 11 studies for inclusion in the review. Study selection is presented in a flow diagram in Fig. 1. The 11 included studies evaluated 8 early detection initiatives. (Three different evaluations of one initiative, the Scandinavian TIPS Programme18-20 and two evaluations of one initiative at the Australian EPPIC service21,22 were conducted.) Outcomes for number of referrals or DUP were reported from seven of the eight initiatives: in the Irish DETECT initiative,23 only the impact on referrers’ behaviour was reported.

Excluded studies comprised studies not concerning early detection initiatives, descriptive reports not evaluating early detection initiatives, review articles, secondary reports of included studies and duplicates. Two studies of some relevance were excluded from this review because they lacked any comparison
Evaluations of the OPUS Project in Denmark\textsuperscript{24} and the PEPP service in Canada\textsuperscript{25} assessed DUP and numbers of referrals at newly established early intervention services over the first 3 years of their operation. Findings from these two studies are discussed.

### Types of early detection initiative

Details of the eight early detection initiatives evaluated by studies included in this review are provided in Table 1.

Three initiatives involved GP education campaigns. Two UK studies, REDIRECT\textsuperscript{26} and LEOCAT,\textsuperscript{27} provided an educational workshop to GP practices and follow-up contact. The workshop involved a video presentation, oral information and distribution of leaflets about early signs of psychosis and where to refer. An Irish study, DETECT,\textsuperscript{23} sent information packs to all GPs within the study area and conducted workshops for large groups of GPs. All three GP education initiatives focused on improving GPs’ awareness of the signs and symptoms of early psychosis and encouraging prompt referral to early intervention services.

One initiative involved service configuration: two of the included studies\textsuperscript{21,22} evaluated the newly established EPPIC service in Australia, which was a dedicated service for people with first-episode psychosis and sought to provide a clear point of referral and swift service response. The establishment of this service was reported as accompanied by some advertising to health professionals and other community organisations, but these activities were briefly described and appear to have been small-scale and informal in comparison to initiatives categorised as multifocus.

Four initiatives linked to local early intervention services were multifocus. The TIPS Project in Norway\textsuperscript{18–20} was the most extensive, running for 4 years in two healthcare sectors. It provided face-to-face training for GPs and other health professionals and visits twice a term to every school in the study area, providing information to teachers, counsellors and pupils. Help-seeking and knowledge about psychosis were promoted to the general public through information distributed directly to households and advertising and information in mainstream media. The campaign’s primary message concerned the benefits of early treatment, but materials were also designed to present a non-frightening, non-stigmatising image of psychosis and mental health services.

The EPIP Project in Singapore\textsuperscript{28} similarly contacted healthcare providers and schools and used mainstream media to engage the general public. Interventions included a docudrama on prime-time television in four languages, advertising on television, radio and newspapers, use of celebrities in media campaigns, public poster and postcard campaigns and the establishment of a telephone hotline for the public to contact for advice or help. The initiative at the PEPP service in Canada\textsuperscript{29} provided written and telephone contact to GPs, visits to school counsellors’ meetings and a public awareness campaign, using posters and distribution of leaflets and other materials in public places and a 30 s television and cinema advertisement. The campaign focused specifically on enhancing awareness of signs of early psychosis, the benefits of early treatment and how to contact PEPP. Attempts to
address negative attitudes to psychosis or mental health services among the general population were not described.29

The EPPIC initiative30 provided face-to-face training to GPs, youth workers and counsellors, aiming to enhance recognition and awareness of symptoms of early psychosis. The initiative also sought to promote help-seeking by young people and their families by providing 12 presentations in 6 schools within the catchment areas. The authors acknowledge that budgetary restrictions limited the EPPIC initiative in terms of promoting help-seeking.30

**Study design and quality**

The characteristics of included studies are reported in online Table DS1.

The 11 included studies comprised two cluster randomised trials, two prospective two-group natural experiments and seven studies which retrospectively compared two groups or one group with a historical comparison. The two cluster randomised trials evaluated GP education initiatives. The two non-randomised prospective studies19,30 evaluated multifocus campaigns. All studies evaluating the impact of service configuration used retrospective study designs. Duration of untreated psychosis was the most commonly assessed outcome, measured by ten studies. The quality of studies included in the review was compromised by several factors. All nine non-randomised studies either did not measure any differences or were unable to adjust in analyses for measured differences between the intervention and comparison areas. Only 4 of the 11 studies were prospective evaluations. Only six of ten studies which measured DUP obtained data from an adequate number (defined as over 60%)17 of eligible patients. Two studies did not report how DUP (onset of psychosis and start of treatment) was defined. Of the ten studies which measured DUP, six did not report using a published assessment tool to elicit information about DUP. Overall, only two studies19,30 were prospective evaluations, based comparisons of DUP on data from a reported, adequate proportion of all eligible patients and clearly defined how DUP was measured. One study26 obtained complete data for numbers of referrals from a robustly designed cluster randomised study. Full description of the quality assessment of studies included in this review is provided in online Table DS2.

**Study results**

Results from included studies regarding DUP and numbers of referrals are presented in online Table DS3.

Significant reductions in mean or median DUP were reported for two out of four multifocus campaigns – from all evaluations of the Norwegian TIPS Project (P = 0.005, P = 0.003, P < 0.005) 18–20 and the EPIP Project in Singapore (P = 0.002).24 Two multifocus campaigns, at the EPPIC service in Australia20 and the PEPP service in Canada,28 found no significant difference in DUP in the campaign and comparison areas. No studies evaluating GP education campaigns or changes in service configuration found
a significant reduction in mean or median DUP from the early detection initiative.

No study found clear evidence of an increase in the number of people with first-episode psychosis referred to services following an early detection initiative. REDIRECT,26 a cluster randomised trial of a GP education programme, found no significant difference in the number of referrals from GP practices in the intervention and control groups. The large-scale, multifocus interventions conducted by the TIPS Project19 and PEPP service29 reported similar incidence rates of treated cases of first-episode psychosis in regions exposed to the campaigns and comparison areas (TIPS: intervention, 50:100 000 v. control, 66:100 000; PEPP: intervention, 27.5:100 000 v. control 26:100 000).

Other outcomes measured by included studies were patients’ pathways to care and their health status at admission and referers’ behaviour. Four studies evaluated pathways to care. For one GP education initiative, REDIRECT,26 and one mass campaign at the PEPP service,29 no significant difference with comparison groups was found in referral source. However, one UK GP education initiative, the LEOCAT study,27 found that patients from GP practices receiving the intervention were less likely to have contact with Accident and Emergency (A&E) departments in their pathway to mental health services. One multifocus initiative, the EPIP Project in Singapore,29 found during the campaign that patients were significantly more likely to self-refer and less likely to be referred via the police than in the historical comparison period.

Five studies measured the severity of illness of patients with first-episode psychosis at first service contact. Patients from areas exposed to a multifocus intervention were found to have significantly less severe symptoms than those from comparison groups in the TIPS Project19,26 and the EPPIC service.30 No significant difference in patients’ symptom severity was found between intervention and comparison areas in the PEPP service however.29 The REDIRECT study26 found no significant difference in symptom severity or premorbid adjustment between patients admitted from areas included in a GP education campaign and comparison areas.

All three studies of GP education initiatives included in this review found some evidence of impact of the initiative on GPs’ referral behaviour. DETECT23 and LEOCAT27 found that GPs receiving education were more likely to refer people with first-episode psychosis to mental health services than GPs in a comparison group. REDIRECT26 found that the time from patients’ first contact with GPs to referral to early intervention services was significantly shorter in duration for patients from GP surgeries in the intervention arm of the study.

Discussion

Understanding the results

Two negative findings regarding early detection strategies are suggested by current evidence. First, two randomised studies20,27 suggest that educating GPs about psychosis and referral procedures may have some impact on service delays once help-seeking has been initiated – and therefore could form a useful part of a broader initiative to reduce DUP – but by itself is insufficient to significantly affect overall DUP or numbers of referrals of people with first-episode psychosis. Second, establishing early intervention services probably does not on its own reduce DUP. The apparently shorter DUP found at the EPPIC early intervention service compared with standard services by Yung and colleagues22 was not assessed for statistical significance and was not replicated by a more robust evaluation of the same EPPIC service.21 Negative conclusions regarding the impact of service configuration on its own are corroborated by the finding from the TIPS study,20 where the positive impact on DUP of establishing an early intervention service at the same time as running a public awareness campaign dissipated once the awareness campaign was discontinued. Two studies excluded from this review24,25 also did not find any reduction in DUP or increase in referral numbers over the first 3 years of an early intervention service’s operation.

Evidence regarding the components of DUP may explain these negative findings. About half of DUP may occur before any help-seeking from health services is initiated.5,27 Changing service configuration or educating health professionals can only affect how promptly treatment is provided once someone with first-episode psychosis has come to health services’ attention. Early detection strategies which limit their focus to reducing service delay may be insufficient to significantly influence DUP as a whole. An additional focus on enhancing help-seeking behaviour by people with developing psychosis or those already in contact with them may be required.

The evidence regarding the effectiveness for early detection of multifocus campaigns is more equivocal. The Norwegian TIPS18-20 and Singapore EPIP28 initiatives showed a positive impact in reducing DUP, while the multifocus campaigns at the Australian EPPIC29 and Canadian PEPP29 services did not. Differences in baseline DUP do not help explain the disparity in outcomes. The TIPS campaign was successful in reducing DUP despite a median DUP in the comparison area of 16 weeks,39 which was comparable to that in the EPPIC study (15 weeks)30 and briefer than that in the PEPP study (22 weeks).29 Positive findings do not simply reflect that it is easier to reduce DUP in areas where it is lengthy to begin with.

Krstev and colleagues30 note the (non-significantly) shorter median DUP in the mass campaign area of their study and the significantly greater incidence of patients with a very long DUP of over 3 years in the intervention area. They suggest that the EPPIC mass campaign’s negative results regarding DUP may in part reflect the campaign’s identification of a number of patients with long DUP who would otherwise never have come into treatment. This is unproven, however, and not supported by the comparable incidence rates for treated cases in intervention and comparison areas reported by the TIPS19 and PEPP29 studies.

Variation in outcomes for DUP following multifocus campaigns may be explained by the content and intensity of the different campaigns. Compared with the unsuccessful PEPP29 and EPPIC30 early detection initiatives, the successful TIPS19 and EPIP28 projects were characterised by: greater overall intensity; more use of mainstream media; greater targeting of the general public in addition to groups of professionals; and more emphasis on promoting help-seeking and changing attitudes to psychosis, not just increasing knowledge about symptoms and services. In order to achieve significant reductions in DUP, multifocus campaigns may require vigorous targeting of barriers to initiating help-seeking as well as reduction in service delays. The conclusion that changing public attitudes and behaviour regarding psychosis may require high-intensity initiatives has some support from wider mental health promotion literature. The Mental Health First Aid initiative developed in Australia has reported greater success in changing beliefs about treatment for and social distance from people with mental illness generally than schizophrenia in particular.31 A 3-year German anti-stigma campaign reported only a small positive impact on public attitudes to psychosis.32 A review of mental health anti-stigma campaigns concluded that changes in attitudes may be modest and hard to sustain and that campaigns including education and contact with a person with mental illness are more effective than education alone.33
Limitations
This review reflects knowledge about initiatives to shorten DUP now that a first generation of studies prompted by the development of early intervention aims and services have reported. However, the strength of current evidence is limited by the modest number of relevant studies, variation in the nature of early detection initiatives and comparison services and the quality of studies. Evaluation of early detection campaigns, where the unit of comparison is services or catchment areas rather than individuals, is inherently problematic. Considerable practical difficulties exist in recruiting sufficient numbers of large areas for cluster randomisation, ensuring that campaigns reach only intervention areas – thus avoiding cross-contamination – and in adjusting for confounding differences between intervention and comparison areas. Conclusions about the effectiveness of early detection campaigns can therefore only be provisional.

Three limitations to the appraisal of studies by this review concern: the descriptive typology of early detection initiatives; the quality assessment of included studies; and the synthesis of study results.

Campbell et al describe types of complex intervention to improve health.44 Green and colleagues distinguish modes of delivery of health education, describing communication of information, interactive training and organisational development.55 These descriptions were used, in the absence of an established typology, to inform the development of two domains used to categorise early detection initiatives in this review. However, these broad descriptive categories may fail to distinguish important differences between interventions.

Given the very limited evidence base, all types of study evaluating early detection initiatives were included in this review to avoid ignoring available evidence. The quality assessment measure used in this review56 was recommended in a review of quality assessment measures55 as suitable to use with randomised and non-randomised studies. Important factors affecting study quality are described in this review and used to consider the strength of available evidence. However, the basis on which to do this is imprecise and studies of higher and lower quality overall are not systematically distinguished.

Meta-analysis of data from different studies was precluded by the nature of reported DUP data (skewed mean DUP data or median DUP lacking information about variance). Meta-analysis may anyway have been inappropriate for the studies in this review. Its implied precision about effect sizes and confidence intervals would have been misleading because of: the moderate quality of included studies; variation between studies in how a key outcome – DUP – was defined and the validity of DUP measures; and the substantial heterogeneity between studies in the nature of comparison standard services and the content of early detection interventions. The review’s narrative synthesis of available evidence does reveal gaps in knowledge and indicate the direction and strength of current evidence and, by comparing successful and unsuccessful interventions, helps consideration of the mechanisms which may influence the effectiveness of early detection initiatives.

Research implications
More good-quality studies are needed for all types of early detection initiatives to strengthen the limited current evidence base. Cluster randomised studies are desirable where possible. Future studies should at least be prospective. A consensus is also desirable about how to measure DUP. Recommendations for DUP measurement37 – for studies to use a standardised assessment measure, to base ratings on multiple informants and to assess reliability of raters’ measurements – have not been consistently adhered to by studies included in this review. Direct comparison of results from studies in this review is hampered by variation in exactly what was being measured and how. (Description of DUP measurement methods used is provided in online Table D54.) Early intervention services have been relatively successful in implementing routine data collection, for example both in the UK through the MiData Project38 and in New Zealand.39 Robust, routine collection of data regarding DUP, pathways to care and other baseline information for people with first-episode psychosis may make it substantially easier to carry out large-scale evaluations of initiatives at catchment area, regional or even national levels.

There is a particular need for studies in three areas relevant to early detection where there is a lack of current evidence. First, no studies found by this review described youth-focused initiatives (e.g. targeting pupils at schools, colleges and universities, including using youth-focused media such as advertising on social-networking sites). Second, no studies evaluated initiatives directed primarily at non-health community professionals (e.g. teachers, school counsellors, youth workers, housing or employment service staff, cultural or faith group organisers). Initiatives targeting young people or non-health service professionals might enhance help-seeking behaviour and, by encouraging direct contact with early intervention services, could also reduce service delays. Both approaches therefore merit investigation. Third, although evidence suggests that establishing dedicated services for people with first-episode psychosis does not by itself reduce DUP, the impact on DUP of services for people with prodromal or at-risk mental states is unclear. Services which aim to prevent transition to psychosis, when they fail in their primary aim, might still fulfil a useful function in ensuring that prompt treatment is delivered once psychosis begins. However, evaluation of psychosis prevention services for people with at-risk mental states has concentrated on outcomes (beyond the scope of this review) for these individuals and their rates of transition to psychosis. We found no studies which evaluated the impact of a psychosis prevention service on mean or median DUP for people with first-episode psychosis across a whole geographical population.

In addition to assessment of the impact of initiatives on number of referrals and length of DUP, early detection campaigns could be informed by a focus on three other key areas by future studies.

First, attention should be paid to the components of DUP as well as its overall duration. The REDIRECT study26 in Birmingham, UK, for example, produced apparently contradictory findings that a GP education initiative prompted swifter referrals of people with first-episode psychosis to mental health services by GPs but had no significant effect on patients’ overall DUP. Not all patients in the study consulted their GP during their pathway to care; an examination by Brunet and colleagues of the components of DUP for patients in the local service system40 also helps explain this finding. Delays within primary care formed only a small proportion of overall DUP, considerably less than delays both in initial help-seeking and within mental health services. This suggests that, in Birmingham, primary care was not a promising target for an intervention to reduce DUP among people with first-episode psychosis. Brunet et al also found that mental health service delays comprised several distinct components, each of which might require a different approach. These included transfers between services (community mental health teams (CMHTs) to early intervention), waiting times for an initial appointment and subsequent delays in achieving treatment with antipsychotic medication.40 The components of DUP are likely to vary across different areas, countries or service configurations.
If the important components of DUP within a target area are understood, local early detection initiatives can be planned accordingly for maximum effect.

Second, outlying cases are important in consideration of DUP. In this review, studies typically found a substantially longer mean DUP than median DUP, with the mean inflated by a small number of cases with very long DUP of several years. A number of studies found that even in the comparison services, median DUP was less than 21, 28 or close to 30 the World Health Organization's 3-month target for median DUP. Some early detection campaigns also reported identifying more patients with very long DUP, some of whom may not have come to the attention of standard predictors of help-seeking for emotional problems.41 An initiative for such initiatives in mental health settings. Many of the factors most promising means to enhance early detection of psychosis. However, knowledge is limited about optimal content and media for such initiatives in mental health settings. Greater understanding of the characteristics of people with long DUP and how they are eventually initiated into treatment could inform interventions specifically to achieve this aim.

Third, future evaluations of any type of early detection initiative should assess patients' pathways to care and experience of initial service contact. Even if early detection initiatives have no effect on the number of referrals or DUP, they might reduce costs or increase patient satisfaction if they lead to reduced contact with police, A&E and in-patient services during pathways to care. Because early experiences of mental health services may have enduring influence on engagement, providing an initial contact with services which is acceptable to patients is of particular importance. Current evidence is insufficient to establish whether early detection initiatives have any such effect.

**Clinical implications**

Studies in this review found that service delays in providing appropriate treatment for people with first-episode psychosis can be considerable, within mental health services as well as between primary and secondary care. The REDIRECT study in the UK, for example, found substantial inconsistency in care pathways for people with first-episode psychosis following referral to mental health services: over 30% (54/179) of eligible patients in the study were not referred promptly to the local dedicated first-episode psychosis services by CMHTs.29 Minimising mental health service delays and barriers to effective treatment is an important goal for mental health services but is probably insufficient to reduce DUP significantly.

Despite strong recommendations in policy guidance that service planners and managers attend to early detection and prompt treatment provision for people with first-episode psychosis, what else they should be doing to facilitate this is unclear from current evidence. General practitioner education campaigns appear by themselves to be ineffective. Campaigns targeting community professionals or young people are of interest and potential value; such initiatives lack current evidence of effectiveness, however, and should therefore be accompanied by rigorous evaluation.

Current evidence suggests that intensive, large-scale multi-focus initiatives including public awareness campaigns are the most promising means to enhance early detection of psychosis. However, knowledge is limited about optimal content and media for such initiatives in mental health settings. Many of the factors which predict active help-seeking in mental health are not easily amenable to change. Being female and experiencing severe psychological distress have been identified as the strongest predictors of help-seeking for emotional problems.41 An empirically based model of help-seeking identified some people as predisposed to self-concealment (keeping personally distressing information from others) and less likely than others to seek help. More promisingly, contact with someone with a mental health problem who has sought professional help has been found to be influential in reducing stigma43 and encouraging help-seeking for emotional problems. The conclusion of a study of stigma campaigns, that the stories and experiences of people who live with mental health problems should be to the fore, may also apply to early detection campaigns. Prominent service user involvement may be needed.

Findings from general medicine may also usefully inform the content of early detection initiatives for psychosis. Other areas of health associated with stigma and with a youthful target population, such as smoking and sexual behaviour, also suggest that intensive, multicomponent awareness campaigns may be most effective.44–46 In the light of mixed evidence regarding the effectiveness of initiatives to reduce treatment delay for heart attack,47 Turner compared successful and unsuccessful initiatives. Features of successful campaigns with potential relevance for psychosis were that: they involved a full range of media; they included accurate portrayal of a comprehensive set of early symptoms – not just the most common ones; and they advised assertively going to seek help if response to a telephone call was not immediate. A review of initiatives to promote early presentation for cancer suggests that initiatives targeting individuals who are at risk, as well as whole-community interventions, may be effective.48

Whatever their content, large initiatives involving public awareness campaigns cannot easily be planned and run by individual services or local service planners. They may be more efficient and effective with organisational leadership and resources from regional or NHS planners. This presents a challenge for macro-level mental health service delivery and organisation if the goal of early intervention for psychosis is to be fully realised.

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**References**


# Table DS1 Characteristics of Included Studies

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<th>Outcomes</th>
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<td>LEQCAT27</td>
<td>Cluster randomised trial &amp; GP practices (23 on each arm)</td>
<td>Age 16-35 with first-episode psychosis</td>
<td>DUP of referred patients with first-episode psychosis referred directly by GP to mental health services in each arm. Proportion of patients using A&amp;E or in-patient services before referral to EIS.</td>
</tr>
<tr>
<td>REDIRECT26</td>
<td>Cluster randomised trial</td>
<td>Age 14–30 with a diagnosis of first-episode psychosis</td>
<td>No primary diagnosis of substance use, mood disorder or organic mental disorder; current criminal proceedings; serious concurrent physical illness; institutional residence; or intellectual difficulty</td>
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<td>DETECT</td>
<td>Two-group retrospective comparison: questionnaire sent to all 365 GPs within study catchment area. Responses from GPs receiving education intervention compared with GPs who did not</td>
<td>All patients with suspected first-episode psychosis</td>
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<td>EPPIC 1a</td>
<td>Historical comparison: 51 EPPIC patients admitted in 8-month period compared with 51 matched patients from 3 previous years with standard mental health services but no EIS team. Patients matched on age, gender, diagnosis, marital status and premorbid functioning</td>
<td>Age 16–30, with first-episode psychosis and no previous treatment</td>
<td>DUP</td>
</tr>
<tr>
<td>EPPIC 1b</td>
<td>Two-group retrospective study</td>
<td>51 EPPIC patients admitted in 8-month period compared with 51 matched patients from 3 previous years with standard mental health services but no EIS team.</td>
<td>No intellectual disability, organic mental disorder, epilepsy or consent to study participation</td>
</tr>
<tr>
<td>TIPS a</td>
<td>Historical comparison: EIS team with early detection campaign compared with standard mental health services with no EIS team. First 2 years of early detection campaign compared with same period 3 years previously.</td>
<td>Age 15–65, with diagnosis of psychosis</td>
<td>Number of patients with first-episode psychosis referred to care and comparison of symptoms (PANSS scoring at admission)</td>
</tr>
<tr>
<td>TIPS b</td>
<td>Two-group, non-randomised prospective comparison study</td>
<td>Age 15–65, with diagnosis of psychosis</td>
<td>Characteristics of patients at admission (symptoms, diagnosis, drug and alcohol use, premorbid functioning)</td>
</tr>
<tr>
<td>TIPS c</td>
<td>Historical comparison: EIS team with early detection campaign compared with standard mental health services including EIS team.</td>
<td>As TIPS a</td>
<td>As TIPS a</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Initiative</th>
<th>Study design</th>
<th>Criteria for including patients in study evaluation</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| EPPIC 2<sup>20</sup> | Two-group, non-randomised prospective comparison study
Comparison = EIS and mobile detection unit but no mass campaign
Study period: 1 year | Age 16–30, with first-episode psychosis and no previous treatment for psychosis
No intellectual difficulties, organic mental disorder; must be English speaking and have stable accommodation | DUP
Characteristics of patients at admission (symptoms, diagnosis) |
| PEPP<sup>23</sup> | Historical comparison
Comparison = EIS team without early detection programme
Study period: 2 years pre- and post-EIS team | Age 16–30, diagnosis of non-affective psychosis
Treatment with antipsychotics <1 month
Consenting to treatment in service | DUP
Referral source (hospitals, community health services, non-health services)
Characteristics of patients at admission (symptoms, diagnosis, premorbid adjustment) |
| EPIP<sup>28</sup> | Historical comparison: 2 years
of an early detection initiative compared with 1 previous year of standard services with no EIS team | First-episode psychosis
No previous psychiatric consultation
No physical cause for psychosis
No drug-induced psychosis | DUP
Referral source: number of family or self-referral, GP, counsellor, police
Characteristics of patients at admission (diagnosis) |

GP, general practitioner; EIS, early intervention service; DUP, duration of untreated psychosis; A&E, Accident and Emergency department; CMHT, community mental health team.
<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias</th>
<th>Allocation bias</th>
<th>Confounders</th>
<th>Data collection methods</th>
<th>Withdrawals</th>
<th>Analysis</th>
<th>Intervention integrity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEOCAT27</td>
<td>Strong</td>
<td>Strong Cluster randomisation by statistician independent of study team (method not stated)</td>
<td>No differences between groups measured prior to intervention</td>
<td>Strong Data collection tools stated</td>
<td>DUP defined</td>
<td>Weak DUP data gathered for 71/197 eligible patients (only patients who saw GP during period of DUP included in analyses)</td>
<td>Study size informed by power calculation DUP data was log transformed to account for skew</td>
</tr>
<tr>
<td>REDIRECT26</td>
<td>Moderate</td>
<td>Strong Cluster randomisation: masked allocation using computer algorithm</td>
<td>Included practices stratified by list size and PCT</td>
<td>Strong Data collection tools stated</td>
<td>DUP defined</td>
<td>Weak for DUP data gathered for 83/179 eligible patients Strong for number of referrals</td>
<td>Study size informed by power calculation Method of analysis/account for skew in DUP data not reported Primary outcome stated in advance</td>
</tr>
<tr>
<td>DETECT23</td>
<td>Strong</td>
<td>Strong Cluster randomisation by statistician independent of study team (method not stated)</td>
<td>No differences between groups measured prior to intervention</td>
<td>Weak, unpublished questionnaire</td>
<td>Weak 126/348 GPs returned questionnaires</td>
<td>No primary outcome stated in advance</td>
<td>All GPs received information pack. Only 48% of respondents had attended an information session</td>
</tr>
<tr>
<td>EPPIC 1a21</td>
<td>Weak</td>
<td>Weak Retrospective comparison of two self-selecting groups</td>
<td>No comparison of area variables Patients matched on demographic/clinical variables</td>
<td>Strong Data collection tool stated and DUP defined</td>
<td>Strong DUP data gathered for 102/102 patients</td>
<td>Log transformation and non-parametric tests used to account for skew in DUP data</td>
<td>n/a</td>
</tr>
<tr>
<td>EPPIC 1b22</td>
<td>Weak</td>
<td>Weak Historical comparison</td>
<td>No differences between groups measured prior to intervention. 8-year gap between data collection period for EPPIC group (1993) and comparison group (2001)</td>
<td>Weak Different data collection methods for study arms DUP methods not defined for comparison group</td>
<td>Moderate DUP data gathered for 53/68 eligible patients in comparison group</td>
<td>No statistical analysis; descriptive data only</td>
<td>n/a</td>
</tr>
<tr>
<td>TIPS a24</td>
<td>Moderate</td>
<td>Weak As EPPIC 1b + comparison group only includes patients still known to CMHT 2 years after entry into treatment</td>
<td>No differences between groups measured prior to intervention Population reported as stable</td>
<td>Moderate DUP defined Assessment involved patient and family; assessment tool not reported</td>
<td>Weak Number of eligible patients not included in study not reported Overall 4-year TIPS inclusion = 53/100 patients, with first-episode psychosis</td>
<td>Non-parametric test used to account for skew in DUP data</td>
<td>Mass campaign implemented</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias</th>
<th>Allocation bias</th>
<th>Confounders</th>
<th>Data collection methods</th>
<th>Withdrawals</th>
<th>Analysis</th>
<th>Intervention integrity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIPS b</td>
<td>Moderate</td>
<td>Moderate Two-group natural experiment</td>
<td>Differences between groups measured Some significant differences found: urban living, rates of immigration, educational attainment – but not accounted for in analyses</td>
<td>Moderate As TIPS a</td>
<td>Moderate DUP data gathered for 281/380 patients</td>
<td>Non-parametric test of median DUP data</td>
<td>Mass campaign implemented</td>
</tr>
<tr>
<td>TIPS c</td>
<td>Moderate</td>
<td>Weak Historical comparison</td>
<td>No differences between groups measured prior to intervention</td>
<td>Moderate As TIPS a</td>
<td>Moderate DUP data collected for 183/229 eligible patients</td>
<td>Non-parametric test used to account for skew in DUP data</td>
<td>Mass campaign implemented</td>
</tr>
<tr>
<td>EPPIC 2</td>
<td>Moderate</td>
<td>Moderate Two-group natural experiment</td>
<td>Areas reported as demographically similar regarding population, gender, average income, education and employment levels</td>
<td>Strong DUP data collected for 98/120 eligible patients</td>
<td>Strong DUP data collected for 169/188 patients</td>
<td>Log transformation and non-parametric tests used to account for skew in DUP data</td>
<td>Mass campaign implemented; possibility of leakage across to control area acknowledged</td>
</tr>
<tr>
<td>PEPP</td>
<td>Strong</td>
<td>Weak historical comparison</td>
<td>No changes to healthcare delivery during the study period; no other comparison of areas reported</td>
<td>Moderate DUP defined Unpublished assessment tool used, based on patient, family and professionals’ reports</td>
<td>Strong DUP data collected for 169/188 patients</td>
<td>Non-parametric test used to account for skew in DUP data</td>
<td>Mass campaign implemented</td>
</tr>
<tr>
<td>EPI</td>
<td>Strong</td>
<td>Weak historical comparison</td>
<td>No differences between groups measured prior to intervention</td>
<td>Weak DUP unclearly defined, no assessment tool reported DUP based on interviews with patient and primary caregiver</td>
<td>Weak Proportion of eligible patients included in study not reported</td>
<td>Non-parametric test used to account for skew in DUP data</td>
<td>Mass campaign implemented</td>
</tr>
</tbody>
</table>

DUP, duration of untreated psychosis; GP, general practitioner; PCT, primary care trust; n/a not applicable; CMHT, community mental health team.
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean (s.d.) DUP</th>
<th>Median DUP</th>
<th>Other DUP results</th>
<th>Number of referrals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GP education</strong></td>
<td>240 (537) days (n = 36)</td>
<td>245 (527) days (n = 35)</td>
<td>Not significant</td>
<td>No significant difference between groups in mean days from first contact with GP to referral to or to assessment by mental health services, but significantly fewer patients in the intervention group (6% v. 27%) experienced delays of longer than 6 weeks</td>
</tr>
<tr>
<td><strong>REDIRECT</strong></td>
<td>247 (454) days (n = 47)</td>
<td>234 (291) days (n = 36)</td>
<td>Not significant</td>
<td>Mean days from first help-seeking to reaching EIS significantly smaller in intervention arm (P = 0.002) Intervention mean: 143 days (s.d. = 193) Control mean: 367 days (s.d. = 389) Other service delay measures show no significant difference</td>
</tr>
<tr>
<td><strong>Service configuration</strong></td>
<td>191 (484) days (n = 51)</td>
<td>236.6 (703) days (n = 51)</td>
<td>Significantly greater mean DUP in intervention sample (using log-transformed and non-parametric tests) despite smaller mean. P value not reported</td>
<td>Intervention: 97 referrals Control: 82 referrals No significant difference</td>
</tr>
<tr>
<td><strong>EPPIC 1</strong></td>
<td>191 (484) days (n = 51)</td>
<td>469 (953) days (n = 53)</td>
<td>No test of statistical significance</td>
<td>No significant difference in proportion of patients with DUP &lt; 1 year but significantly more patients in intervention group with long DUP (&gt; 3 years)</td>
</tr>
<tr>
<td><strong>Multifocus initiatives</strong></td>
<td>314 (359) days (n = 40)</td>
<td>254 (801) days (n = 50)</td>
<td>No significant difference in mean or median results</td>
<td>No data presented but authors report probable greater increase in cases in intervention region during study period</td>
</tr>
<tr>
<td><strong>TPS</strong></td>
<td>26 weeks (n = 60)</td>
<td>114 weeks (n = 63)</td>
<td>Mean DUP significantly shorter in intervention group (P = 0.005)</td>
<td>186 eligible patients from intervention regions (incidence over 4 years: 50/100,000) 194 eligible patients from control regions (incidence 66/100,000) No test of significance reported</td>
</tr>
<tr>
<td><strong>TPS</strong></td>
<td>Median DUP significantly shorter in intervention group (P = 0.003). Intervention area was significantly associated with shorter DUP in linear regression</td>
<td>16 weeks</td>
<td>No significant difference in numbers of patients with long DUP (&gt; 2 years)</td>
<td></td>
</tr>
<tr>
<td><strong>TPS</strong></td>
<td>26 (59) weeks (n = 108)</td>
<td>105 (276) weeks (n = 75)</td>
<td>Mean DUP significantly shorter in intervention group (P = 0.005)</td>
<td>More patients in intervention group with very short (&lt; 12 weeks) and very long (&gt; 2 years) DUP, more patients in control group with medium DUP. Significance of differences not tested</td>
</tr>
<tr>
<td><strong>PEPP</strong></td>
<td>No significant difference in median DUP</td>
<td>24 weeks (n = 84)</td>
<td>No significant change in DUP following discontinuation of the intervention</td>
<td></td>
</tr>
<tr>
<td><strong>EP</strong></td>
<td>13 (26) months (n = 287)</td>
<td>32 (59.3) months (n = 107)</td>
<td>Median DUP significantly shorter in intervention group (P = 0.002)</td>
<td>Annual treated incidence rate: intervention group, 27.5/100,000; control group, 26.6/100,000 No test of significance reported</td>
</tr>
</tbody>
</table>

GP, general practitioner; EIS, early intervention service.


**Early detection review – electronic search terms:**

**MEDLINE search**

exp schizophrenia/ OR exp paranoid psychosis/ OR (schizoid$ or psychotic$ or psychosis or psychoses or hebephrenic$ or oligophrenic$).hw,id,tw OR (((chronic$ or severe$) adj5 mental$ adj5 (ill$ or disorders$))).tw

AND

((duration and (((long$ or delay$ or not$1 or wait$) adj2 treat$) or un$treat$) or DUP$1)).tw OR (((decrease$ or lessen$ or lower$ or minimal$ or prevent$ or reduce$ or shorten$) and (((long$ or delay$ or not$1 or wait$) adj2 treat$) or un$treat$))).tw OR early diagnosis/ or exp early intervention/ or “early intervention (education)”/ OR (early adj3 (detect$ or interv$ or diagnos$ or recogni$)).tw OR (client education or health education or health promotion or patient education or psychoeducation).sh,id. OR (((communit$ or health) adj3 (educa$ or promot$))).tw OR (((communit$ adj2 awareness) or ((health or wellness) adj campaign$))).tw OR prodrom$.tw OR early onset.tw

AND

A. [Systematic review filter] (literature searching or (systematic review$ or meta$ or metaanaly$)).sh,id. OR (((analy$ or assessment$ or evidence$ or method$ or quantiti$ or qualitative$ or systematic$) adj5 (overview$ or review$))).tw. or (((analy$ or assessment$ or evidence$ or method$ or quantiti$ or qualitative$ or systematic$)).ti. and review$.ti,pt.). or (systematic$ adj5 search$).ti,ab. OR ((electronic database$ or bibliographic database$ or computerized database$ or online database$)).tw.sh. or (bids or cochrane or index medicus or isi citation or psyclit or psychlit or sci search or science citation or (web adj2 science$)).tw. or (cochrane$.sh.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.) OR (metaanaly$ or meta anal$ or metasynthesis$ or meta synthesis$).ti,ab. OR reference adj (review$ or integration$)).ti,ab. OR reference list$.ab. OR bibliograph$.ab. OR published studies.ab. OR relevant journals.ab. OR selection criteria.ab. OR (data adj (extraction or synthesis$)).ab. OR (handsearch$ or (hand or manual) adj search$).ti,ab. OR (mantel haenszel or peto or dersimonian or der simonian).ti,ab. OR (fixed effect$ or random effect$).ti,ab. OR (systematic$ or meta$).pt. or (literature review or meta analysis or systematic review$).md. OR ((pool$ or combined or combining) adj2 (data or trials or studies or results$)).ti,ab. OR

B. [Randomised controlled trial filter] exp clinical trials/ or exp controlled clinical trials/ or (crossover procedure or double blind procedure or placebo or randomization or random sample or single blind procedure).sh OR exp clinical trial/ or cross-over studies/ or double-blind method/ or random allocation/ or randomized controlled trials as topic/ or single-blind method/ OR exp clinical trials/ or (placebo or random sampling).sh, id. OR exp clinical trials/ or (crossover design or double-blind studies or single-blind studies or random assignment or triple-blind studies).sh, or random sample.tw. OR (clinical adj2 trial$).tw. OR (crossover or cross over).tw OR (((single$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$)).tw. OR (placebo$ or random$).mp. OR (clinical trial$ or random$).pt. or treatment outcome$.md.

OR

C. [Observational study filter] (clinical study or cohort analysis or correlational studies or cross sectional studies or epidemiologic studies or family study or longitudinal study or nonconcurrent prospective studies or prospective study or retrospective study).sh OR exp case control studies/ OR “epidemiological study$”.id or “empirical study$”.md OR ((cross sectional or epidemiologic$ or observational$) adj (study or studies$)).tw OR (case$ or cohort$ or cross sectional or followup$ or follow up$ or followed or longitudinal$ or retrospective study.ori).tw OR (case$ or cohort$.mp OR follow-up$ or follow up$ or longitudinal$ or prospective$ or retrospective$).tw

OR

D. [Grey literature filter] limit to (congresses or government publications or technical report) AND (abstract report$ or book$ or conference paper$ or dissertation$ or government publication$ or pamphlet$ or report$ or theses$).sh. or “policy and procedure manuals$”)). OR ((book$. or brochure$ or dissertation$ or pamphlet$ or report$ or thesis$ or theses$)).tw
<table>
<thead>
<tr>
<th>Initiative</th>
<th>Definition of onset of illness</th>
<th>Definition of start of treatment</th>
<th>Measurement instrument / information sources</th>
<th>Data reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEOCAT27</td>
<td>Two definitions used: “traditional DUP” – time from first psychotic symptom; and “contemporary DUP” – time from unremitting psychotic symptoms for 1 week, using CAARMS criteria22</td>
<td>Two definitions used: ‘traditional DUP’ – first contact with mental health services; and ‘contemporary DUP’ – the commencement of antipsychotic medication (greater than 50% treatment adherence for a minimum of 1 month)</td>
<td>Combined DUP, pathway to care and service receipt measure. Information gathered from patient, carer and clinician</td>
<td>Mean DUP</td>
</tr>
<tr>
<td>REDIRECT20</td>
<td>First week with psychotic symptoms scoring 4 or above on PANSS54 positive symptoms</td>
<td>Start of adequate antipsychotic medication or hospital admission Criteria defined by Larsen et al55</td>
<td>Semi-structured interview based on checklist Patient interviewed; no other sources stated</td>
<td>Mean DUP</td>
</tr>
<tr>
<td>EPPIC 1a21</td>
<td>Onset of sustained symptoms at threshold level</td>
<td>Initiation of treatment Both operationalised in Royal Park Multi Diagnostic Instrument for Psychosis (RPMP); good interrater reliability established57</td>
<td>RPMP Interview with patient and other informant (usually family member)</td>
<td>Mean DUP (EPPIC 1a &amp; 2)</td>
</tr>
<tr>
<td>EPPIC 220</td>
<td>Not defined</td>
<td>Not defined</td>
<td>As EPPIC 1a for EPPIC group No assessment instrument reported for comparison group; source = case notes</td>
<td>Mean DUP</td>
</tr>
<tr>
<td>TIPS a &amp; c18,20</td>
<td>Onset of psychotic symptoms (first week with symptoms corresponding to a PANSS score of 4 or above for positive symptoms)</td>
<td>Start of treatment (start of antipsychotic medication or hospital admission or psychotherapy for psychosis)</td>
<td>Use of assessment instrument not reported All available data sources used including interviews with patient and relatives</td>
<td>Mean DUP</td>
</tr>
<tr>
<td>TIPS b24</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td>Median DUP</td>
</tr>
<tr>
<td>PEPP27</td>
<td>Onset of psychotic symptom (corresponding to structured clinical interview for DSM-IV thresholds)</td>
<td>Start of adequate treatment (taking antipsychotics for 1 month or until treatment response)</td>
<td>CORS (Circumstances of Onset and Relapse Schedule) – unpublished instrument based on RADS29 All sources used to calculate DUP including patient, family and involved professionals’ reports</td>
<td>Median DUP</td>
</tr>
<tr>
<td>Epi28</td>
<td>Onset of psychotic symptoms (no severity or duration specified)</td>
<td>The time when a diagnosis and treatment (unspecified) were established</td>
<td>None stated Information from patient and primary carer</td>
<td>Mean DUP</td>
</tr>
</tbody>
</table>

GP, general practitioner; EIS, early intervention service.
Additional references


Initiatives to shorten duration of untreated psychosis: systematic review

Brynmor Lloyd-Evans, Michelle Crosby, Sarah Stockton, Stephen Pilling, Lorna Hobbs, Mark Hinton and Sonia Johnson

BJP 2011, 198:256-263.
Access the most recent version at DOI: 10.1192/bjp.bp.109.075622

**Supplementary Material**
Supplementary material can be found at:
http://bjp.rcpsych.org/content/suppl/2011/03/01/198.4.256.DC1

**References**
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