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Should people with psychosis be supported in choosing cognitive therapy as an alternative to antipsychotic medication: A commentary on current evidence

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ABSTRACT

Evidence from randomised controlled trials suggest that both antipsychotic medication and cognitive behaviour therapy (CBT) can be helpful to people with a diagnosis of a schizophrenia spectrum disorder. On this basis, many clinical guidelines recommend that people with psychosis should be offered both antipsychotic medication and CBT and that they should be collaboratively involved in the decisions about which treatment options they choose. The reality of service provision is often very different, with data regarding the availability of such treatment options and the extent of user involvement in decision making suggesting that medication is much more widely available and that service users are often not involved in these decisions, despite retaining decision making capacity. Many patients choose not to take antipsychotic medication, often due to inefficacy or side effects, but there is little evidence regarding whether CBT can be effective as an alternative to antipsychotic medication. However, several recent trials suggest that CBT without medication may be a safe and acceptable option for people with psychosis. The implications for clinical practice and future research are considered and it is recommended that informed choices that include the option to try CBT without antipsychotic medication are supported.

1. Introduction

There is good evidence from clinical trials that both antipsychotic medication and cognitive behaviour therapy (CBT) can be helpful to people with a diagnosis of schizophrenia and other psychoses. On this basis, many clinical guidelines from countries around the world suggest that all people with psychosis should be offered antipsychotic medication and CBT and be involved in collaborative decision making about which treatment options they choose (Dixon et al., 2010; Galletly et al., 2016; National Institute for Clinical Excellence, 2013; National Institute for Health and Care Excellence, 2014). However, neither are a panacea and the individual cost-benefit ratios of such treatments will vary considerably, both between individuals and potentially within individuals over time. The cost-benefit ratio of such treatments is a balance between efficacy and adverse effects, so this paper will consider the literature on effectiveness and unwanted effects of both antipsychotic medication and CBT. It will also examine whether there is any evidence that CBT can be delivered to people with psychosis as a standalone intervention, as opposed to as an adjunct to antipsychotic medication. Finally, cost-benefit profiles in the context of patient choice and decision making capacity, and implications for practice and future research will be considered.

1.1. Efficacy of antipsychotics and CBT

Recent meta-analyses of RCTs of CBT for psychosis (Jauhar et al., 2014; Mehl et al., 2015; van der Gaag et al., 2014) have found effect sizes ranging between 0.3 and 0.4 relative to treatment as usual, although these effects sizes reduce when limiting studies to those with the most rigorous trial methodology. Recent meta-analyses of antipsychotic medication relative to placebo have also found effect sizes that range from small to moderate, with the exception of clozapine which has a large effect (S. Leucht et al., 2009; Stefan Leucht et al., 2013). The most comprehensive meta-analysis in chronic schizophrenia reporting a standardised effect size for total symptoms of 0.47, which reduced to 0.38 when publication bias and small-trial effects were accounted for (Stefan Leucht et al., 2017). However, while CBT and antipsychotics demonstrate superiority over comparators (treatment as usual and placebo respectively) to a statistically significant level, the proportion of individuals who achieve a clinically meaningful benefit is modest. The figure will depend largely on subject characteristics and how one defines clinical improvement. For example, a recent meta-analysis

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(Stefan Leucht et al., 2017) showed that 51% of multi-episode patients had at least a minimal response (≥20% reduction in PANSS/BPRS) reducing to 23% when the more stringent criterion of a good response was applied (≥50% reduction PANSS/BPRS). These average effects that are observed in clinical trials will potentially mask the variation in response, with some participants responding much better than others. There is some evidence for different trajectories of response, with a small proportion of patients demonstrating a rapid favourable response to certain antipsychotics (Marques et al., 2011), and non-response in the early weeks of treatment is a strong predictor of eventual antipsychotic non-response (Kinon et al., 2009). Currently, we have to rely on anecdotal evidence regarding trajectories of response to CBT, with some people responding much more rapidly than others to CBT for psychosis. Most RCTs of CBT for psychosis have not reported response for predefined good clinical outcomes, so the proportion who achieve these is uncertain. Therefore, more research is required, both to identify those most likely to respond to CBT and how many can expect good clinical outcomes.

Antipsychotics clearly have an effect on psychotic symptoms, and they also have shown benefits for relapse prevention (Stefan Leucht et al., 2012). In terms of psychological interventions, the largest trial of CBT for psychosis to examine relapse prevention found no benefit of CBT in comparison with treatment as usual. However, family intervention has consistently been shown to have benefits for relapse prevention (National Institute for Health and Care Excellence, 2014). The effects of antipsychotic medication on functioning and quality of life are less clear than for symptoms and relapse prevention. For example, functional outcome at 7 years was better in people with first episode psychosis who were randomised to stop antipsychotic medication versus those who continued medication, suggesting that antipsychotics may cause poor long-term functional outcomes (Wunderink et al., 2013), and 20-year outcome data from the Chicago Follow-Up study suggests that patients who decide not to take antipsychotics (often against medical advice) do relatively well, if not better, in comparison with those who take such medication continuously (Harrow et al., 2012). Another study found remitted first-episode patients who had their second-generation antipsychotics gradually withdrawn experienced significant improvements in neurocognitive functioning when compared to those who continued with maintenance treatment (Faber et al., 2012). There is also evidence that antipsychotics can cause negative symptoms in healthy volunteers (Artaloytia et al., 2006).

1.2. Adverse effects of antipsychotics and CBT

Adverse effects of antipsychotics are well known. These include an increased risk of sudden cardiac death (Ray et al., 2009), and increased cardiovascular risk is even detectable after the first exposure to any antipsychotic medication (Foley and Morley, 2011). There is also indisputable evidence regarding weight gain induced by antipsychotics (Alvarez-Jimenez et al., 2008), which is also likely to be relevant to cardiovascular risk and mortality and is clearly implicated in the increased risk of metabolic disorders such as diabetes (Teff et al., 2013). There is growing evidence regarding loss of grey matter and other structural brain abnormalities (Ho et al., 2011; Moncrieff and Leo, 2010; Vita et al., 2015). There are also many other side effects including sedation, sexual dysfunction, parkinsonian symptoms, movement disorders and hyperprolactinemia (Haddad and Sharma, 2007), as well as subjective side effects such as impaired ability to think and experience emotions (Moncrieff et al., 2009). There is also evidence that some of these side effects are more problematic for adolescents than for adults (Correll et al., 2009; Kryzhanovskaya et al., 2012).

Adverse effects for CBT for psychosis have not been well studied (Jauhar et al., 2014) and it is clear that researchers need to improve in their monitoring of potential adverse effects of talking therapies. However, side effects that have been suggested to be likely, such as stigma and deterioration of mental state (Taylor and Perera, 2015), have not been found when they have been measured in clinical trials of CBT for people with psychotic experiences; in fact, CBT can result in significant reductions (Morrison et al., 2013; Morrison et al., 2014). However, there is some evidence that CBT delivered in the context of a poor therapeutic relationship may be harmful (Goldsmith et al., 2015).

1.3. Acceptability and availability of antipsychotics and CBT

The acceptability of CBT and antipsychotic medication is also likely to be different for different people. Evidence from qualitative studies suggest that CBT for psychosis seems acceptable (Wood et al., 2015), whereas it is clear from qualitative studies that many people discontinue antipsychotic medication for a variety of reasons including lack of efficacy, incompatibility with personal beliefs and side effects (Wade et al., 2017). Quantitative data from trials suggests that dropout from CBT for psychosis is relatively low (Szymczynska et al., 2017), while discontinuation rates for antipsychotics have been estimated to be as high as 40–50% (Lacro et al., 2002):

Thus, both CBT and antipsychotics have the potential to help people with psychosis, but the adverse effect profiles, and associated acceptability, would seem to favour CBT. However, on an individual basis it is impossible to know who will benefit and who will experience adverse effects. Therefore, it would seem appropriate to recommend that all people with psychosis be offered access to both treatments (as well as family intervention, where relevant), which is consistent with current clinical guidelines (National Institute for Clinical Excellence, 2013; National Institute for Health and Care Excellence, 2014).

However, the reality of service provision is often very different, and data regarding the availability of such treatment options and the extent of user involvement in decision making is not encouraging. A recent survey in the UK of over 300 service users with psychosis (Carter et al., 2017) found that they were much more likely to have accessed antipsychotic medication than evidence-based and guideline-recommended psychological interventions (CBT or family interventions). The vast majority of these patients were currently receiving antipsychotic medication (88%), whereas only 10% were receiving CBT. Furthermore, less than half reported that they were offered a choice of treatments, although the majority of respondents expressed a desire for choice when making treatment decisions. Similarly, the UK-based Schizophrenia Commission (The Schizophrenia Commission, 2012) also concluded that 'only 1 in 10 of those who could benefit get access to true CBT' and recommended 'greater partnership and shared decision making with service users – valuing their experiences and making their preferences central to a recovery-focused approach'. Much of the research on CBT for psychosis has been conducted in the UK, so it is likely that access elsewhere may be even more challenging. Consistent with this, a large survey of training directors in the US found "minimal awareness of the CBTp evidence-base along with training opportunities that are so limited as to be unlikely to be adequate to provide CBTp effectively" (Kimhy et al., 2013). The generalisibility of CBT for psychosis to other non-western cultures is less clear, although there have been several trials conducted in lower to middle income countries and several adaptations to CBT to make it more acceptable to different ethnic groups.

2. Evidence for CBT without antipsychotics

While the vast majority of evidence for efficacy of CBT for psychosis is from randomised controlled trials where CBT is provided in addition to treatment as usual, which is usually antipsychotic medication. However, there are several recent or current clinical trials that address the question of whether CBT can be effective for people with psychosis who are not taking antipsychotic medication. Initially, there were some promising case studies and case series that suggested that CBT might be helpful without antipsychotics (Christodoulides et al., 2008; Morrison, 1994, 2001). These were followed by an open trial of 20 patients with schizophrenia spectrum disorders who had chosen not to

take antipsychotics, which found that CBT appeared to have beneficial effects on psychotic symptoms, total psychiatric symptoms, social functioning and recovery (Morrison et al., 2012). Subsequently, a larger randomised controlled feasibility trial ($n = 74$), established the safety and acceptability of using CBT as an alternative to antipsychotics in people who had chosen not to take them (Morrison et al., 2014). This trial also found that participants allocated to CBT improved significantly on overall psychiatric symptoms (PANSS total), dimensions of psychotic symptoms and social functioning over 18 months. There were very few deteriorations in mental state (and less in the CBT arm than treatment as usual), no compulsory admissions in the CBT arm and no serious adverse events related to CBT or trial participation. Commentary on this trial suggested: 'findings provide proof of concept that cognitive therapy is an alternative to antipsychotic treatment. Clearly this outcome will need further testing, but, if further work supports the relative effectiveness of cognitive therapy, a comparison between such therapy and antipsychotic treatment will be needed to inform patient choice' (Howes, 2014). The COMPARE trial (ISRCTN06022197), a single site RCT in the UK, has recruited to target, randomising 75 participants with psychosis (73 of whom were experiencing their first episode of psychosis) to CBT, antipsychotics or a combined treatment and will assess symptoms, functioning and adverse effects over 12 months. This trial demonstrated that CBT alone, as well as combined treatment and antipsychotics alone, were all safe and acceptable and resulted in significant improvements over a 12 month period (Morrison et al., 2018). While this trial did not have sufficient statistical power to definitively answer questions of relative efficacy and effectiveness, there were strong suggestions that the combined intervention was superior to both monotherapies in terms of severity of total psychiatric symptoms and that CBT alone was superior to both conditions involving antipsychotics on side effects. However, there was no suggestion of any difference between CBT alone and antipsychotic medication alone in their effects on total symptoms. The STAGES trial (ACTRN12607000608460), is currently underway in Australia; this is a RCT which is comparing CBT plus placebo with CBT plus antipsychotic medication in 95 young people aged 15–25 with first episode psychosis on outcomes including both symptoms and functioning over 24 months. The MAPS trial (ISRCTN80567433) is a multisite feasibility RCT examining the effectiveness of CBT plus family intervention compared with antipsychotics and a combined treatment in adolescents with psychosis. This trial aims to recruit 90 participants aged 14–18 with first episode psychosis and evaluate the treatments on outcomes including symptoms, functioning, recovery and adverse effects over 12 months. While these trials are yet to report or still being conducted, all have procedures for detecting and managing deterioration and monitoring safety of participants; to date, there have been no such concerns. Data from the COMPARE trial suggests that such studies are acceptable to participants, with very few people declining once assessed as eligible (Law et al., 2017). Collectively, the outcome data from these trials should provide a body of evidence to begin to inform treatment decisions in first episode psychosis, and certainly demonstrate safety of CBT without medication, although a large definitive trial would still be required to comprehensively assess relative efficacy. It is also important conduct more research in order to determine if any effects generalise to people with more established, long-term psychoses and schizophrenia. However, since most people with longer-term psychosis will have been receiving antipsychotic medication for many years, caution should be exercised given the possibility of withdrawal effects and rebound psychosis.

3. Cost benefit ratios and collaborative decisions

Some patients will benefit a great deal from both CBT and antipsychotics, some benefit from one more than the other, some will respond to a lesser extent to both and some may not benefit at all. The evidence on which current guideline recommendations are based usually consists of aggregate data meta-analyses that result in estimates of average treatment effects averaged across multiple randomised controlled trials (RCTs); this provides confidence about the likelihood of benefits outweighing costs on average, but provides little information about how a particular individual will respond to a particular treatment. Thus, we can be confident that both antipsychotics and cognitive behaviour therapy (CBT) are likely to be helpful in reducing psychiatric symptoms in people with psychosis, but we have little way of knowing whether a specific individual is more likely to benefit from or respond to medication or talking therapy or the combination of the two. Equally, the side effect profiles are likely to differ between these interventions, with the side effect profiles of antipsychotics having led some to question the advisability of routine long-term prophylactic use of antipsychotics (Murray et al., 2016). The individual cost-benefit profiles (balance between effectiveness and side effects) will also be affected by patient characteristics and preferences. For example, a recent individual participant data meta-analysis that combined six antipsychotic trials concluded that the biggest benefits of antipsychotics were seen in the most severe cases, and that, at "the mildest end of the spectrum, clinicians need to be aware that patients benefit less in terms of symptom improvement but may experience full adverse effects of antipsychotics" (Furukawa et al., 2015).

Patient preference and informed choice is also essential to consider, given that they routinely express a strong desire to be included in treatment decisions and to have access to options and alternatives including talking therapies (Warner et al., 2006). People with psychosis and schizophrenia also have strong preferences and opinions regarding the most important and valued outcomes (Byrne et al., 2010), which are often prioritising affective and functional outcomes over positive symptoms (Moritz et al., 2017).

Making collaborative decisions and informed choices on the basis of likely cost-benefit profiles requires decision making capacity. A recent systematic review and meta-analysis found that many patients with a diagnosis of schizophrenia retain decision making capacity, even when requiring inpatient care (Spencer et al., 2017). Another recent systematic review and meta-analysis has found encouraging results for shared decision making interventions to improve ability to be meaningfully involved in decisions about treatment (Stovell et al., 2016). A study examining decisions about antipsychotics in people with schizophrenia-spectrum disorders found that refusing medication after a phase of initial adherence was often the consequence of negative experiences with medication and often results from a rational weighing up of the risks against the benefits (Lincoln et al., 2016). Therefore, if people with psychosis choose not to take antipsychotic medication, it is important to have evidence-based alternatives available to them, so an increased emphasis on dissemination and implementation, especially outside the UK, is required. However, CBT for psychosis is an expensive therapy since it is often delivered over 6–12 months and requires a high level of clinical skill and most trials have used highly qualified professionals. Therefore, it will require significant financial investment to improve access and ensure availability. This investment may be offset by cost savings such as reductions in hospital admissions and increases in proportions of people with psychosis in employment, education or training.

4. Implications for future research

More research is needed to inform our ability to predict those most (and least) likely to respond to both antipsychotics and CBT. Statistical analyses of response trajectories from existing drug trials and CBT trials would help to address this issue. Similarly, once there are head-to-head trials of CBT compared to antipsychotics, analysis of moderators of treatment response will be informative. Similarly, individual participant data meta-analyses will be able to inform our understanding of patient characteristics that will be modifiers of treatment response, as would cohort studies that utilise momentary assessment techniques such as

experience sampling methodologies to evaluate the effects of treatments in the early weeks of engagement. Such methodologies should help us address the burning question of what works for whom?

Other than the trials mentioned in Section 2, there is no evidence regarding the relative efficacy of these treatments, and a recent Cochrane review concluded that there was no usable data to answer the question of whether antipsychotic medication or psychosocial interventions are required for first episode psychosis (Bola et al., 2012). Therefore, a large, definitive randomised controlled trial would be required to answer questions regarding relative clinical and cost-effectiveness of CBT and antipsychotics in head-to-head comparisons. However, it is uncertain as to what the most appropriate primary outcome should be for such trials, given the differences of opinion regarding definitions of recovery, with clinicians prioritising symptom reduction (such as positive symptoms or total symptoms of schizophrenia) and service users prioritising functioning, quality of life and more holistic recovery that incorporates hope, connectedness and empowerment (Leamy et al., 2011).

5. Implications for clinical practice

It is time to reject the assumption that antipsychotics must always be the first line of treatment for people with psychosis; rather, this should be a collaborative decision that is based on informed choices and the availability of evidence-based alternative treatments. These decisions should be negotiated with service users on the basis of the likely positive, wanted effects and the negative, unwanted effects and the prioritisation of their goals for treatment. At present, it would seem reasonable to support people with psychosis to make such informed choices regarding antipsychotic medication and CBT; in the absence of immediate risk to self or others, this should include the option to try CBT without medication for those who wish to pursue an evidence-based talking therapy without exposure to the adverse effects of medication.

Conflict of interest declaration

AM has received fees and royalties from training workshops and books on CBT for psychosis and delivers CBT for psychosis in the NHS.

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None.

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