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CLINICAL PSYCHOLOGY & NEUROPSYCHOLOGY | RESEARCH ARTICLE

How many clients with refractory psychosis are eligible for both cognitive-behaviour therapy and clozapine? A chart-review study

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Abstract: Substantial evidence supports the use of either clozapine or cognitive-behaviour therapy (CBT) for refractory symptoms of psychosis, and are recommended in many national guidelines. However, the two treatments have not been directly compared in a head-to-head trial. The aim of this study is to estimate the proportion of clients with refractory symptoms of psychosis who might benefit from either treatment. We reviewed the charts of 137 clients, consecutively referred to a speciality clinic for refractory psychosis, against inclusion and exclusion criteria for both clozapine and CBT. The results indicate that approximately one-third of patients referred for either CBT or clozapine would simultaneously meet eligibility criteria for both treatments, and would thus be eligible for randomization. If these results are validated in a prospective study, a controlled trial comparing CBT and clozapine for refractory symptoms of psychosis is likely feasible.

Subjects: Behavioral Sciences; Health and Social Care; Medicine, Dentistry, Nursing & Allied Health

ABOUT THE AUTHORS

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PUBLIC INTEREST STATEMENT

When standard treatments for psychosis are not effective, and symptoms of psychosis persist, national treatment guidelines suggest two validated treatment strategies: a medicine called clozapine, or cognitive behaviour therapy (CBT). The treatment guidelines do not offer any guidance to clinicians as to which one to use, or indeed if there are clients for whom both treatments would be helpful. As a first step toward a controlled comparison of the two treatments, we conducted a review of 137 consecutive referrals in our speciality clinic for clients with persistent psychotic symptoms. We examined the referrals that requested clozapine or CBT, to determine the number of clients who were eligible for both treatments. The results suggest that approximately one-third of clients would be eligible for both. If these results are replicated, then a controlled trial may be feasible, which could provide guidance to clients and their clinical team on the choice between the two treatments.

Keywords: CBT; clozapine; randomized controlled trial; psychosis; refractory symptoms

1. Clinical implications

- a substantial subset of clients with refractory symptoms of psychosis, referred for either CBT or clozapine, may be eligible for both treatments
- the significant number of dually eligible clients means that clinical services should have the capacity to offer both treatments for refractory symptoms
- eligibility for treatment, based on established criteria, needs to be followed by consideration of patient needs and preferences

2. Limitation

- this study is based on chart-review methodology

3. Background

Approximately one-third of people diagnosed with schizophrenia continue to have medication-resistant symptoms even after optimal treatment, although estimates vary widely from 15% to 20% (McGorry, Killackey, Elkins, Lambert, & Lambert, 2003) to 60% (Elkis, 2007; Gillespie, Samanaite, Mill, Egerton, & MacCabe, 2017). The treatment-resistant concept was refined in the late 1980s and early 1990s to aid in the development of new medicines, especially to identify criteria for clozapine. As such, the core features of the concept are defined as pervasive positive symptoms that remain after two or three adequate medication trials, each lasting 4–6 weeks at chlorpromazine-equivalent doses of 1000 mg/day (Suzuki et al., 2012).

Clozapine is widely regarded as a treatment of choice for clients with refractory symptoms of psychosis (Haddad & Correll, 2018; National Institute for Health & Care Excellence [NICE], 2014; Siskind, McCartney, Goldschlager, & Kisely, 2016), especially in longer-term and non-industry-funded studies, and compared to first-generation antipsychotic medicines (Samara et al., 2016; Siskind et al., 2016). For a significant proportion (30–40%) of these clients, however, clozapine either does not provide significant improvement or has various adverse side effects that are intolerable (Morrison et al., 2018).

Current treatment guidelines also recommend psychological treatments for people with schizophrenia (NICE, 2014; American Psychiatric Association [APA], 2010). In particular, cognitive-behaviour therapy has shown to be an effective adjunct to non-clozapine medications for a wide variety of patients with schizophrenia, including those with medication-resistant symptoms (Burns, Erickson, & Brenner, 2014). Whether CBT provides improvements for clients already on clozapine is still an open question: two small pilot studies documented short-term improvements in symptoms (Barretto, Kayo, Avrichir, et al., 2009; Pinto, La Pia, Mennella, Giorgo, & DiSimone, 1999). Recently, however, a larger and well-controlled trial of CBT added to clozapine, compared to clozapine-as-usual, found a small effect in favour of CBT at end of treatment, but the superiority did not persist at 21-month follow-up (Morrison et al., 2018).

Despite the respective evidence for improvements in positive symptoms, clozapine monotherapy and adjunctive CBT have not been the subject of a head-to-head trial. Indeed, there are no published data to indicate whether such a study is indeed feasible or whether, for example, the two treatments would be indicated for different subsets of patients with refractory symptoms. The aim of this chart-review study was to examine consecutive referrals to a speciality out-patient clinic to assess eligibility for these two evidence-based treatments, and estimate the proportion of patients who would be eligible for both treatments and thus for a randomized controlled trial.

4. Methods

We reviewed charts of all 137 referrals, in the nine months between May 2016 and January 2017, to our specialized Refractory Psychosis program. The study was approved by the Fraser Health Research

Ethics Board (FHREB 2016–024). The referring clinician can request any of clozapine; CBT; guidance on treatment optimization, e.g. nursing support; or a second opinion from a program psychiatrist.

To be eligible for the program as a whole, referred clients must meet all of the following criteria: age 19–64 years; have a schizophrenia-spectrum or affective psychosis diagnosis; have had adequate trials of two or more antipsychotic medicines, each of which was six weeks or more of at least 300 chlorpromazine-equivalents (CPZ-eq) per day or greater; be experiencing current hallucinations or delusions (i.e. at least two positive symptom ratings of "mild", or one of "moderate" on the Brief Psychiatric Rating Scale; Ventura, Nuechterlein, Subotnik, Gutkind, & Gilbert, 2000); and provide informed consent.

To be eligible for clozapine in our program, one of three additional inclusion criteria was required: (a) current antipsychotic medication at high dose (CPZ-eq ≥600); (b) currently on multiple antipsychotic medications; or (c) global ratings of 50 or less ("serious") on either the symptom or functioning scales of the Global Assessment of Functioning (GAF; American Psychiatric Association [APA], 2000). Exclusionary criteria for clozapine were any of the following: (a) treatment with a long-acting injectable antipsychotic medicine in the past two months; (b) established contraindications, e.g. history of myocarditis, agranulocytosis, diabetes, or compromised hepatic or renal function; (c) a previous trial of clozapine that was interrupted due to side effects or haematological problems; or (d) or metabolic problems or Body-Mass Index greater than 30.

For CBT, the inclusion criteria were a sufficient level of English, and at least a bit of insight (rating of 4 or less on item G12 from the Positive and Negative Syndrome Scale [PANSS]; Kay, Opler, & Fizbein, 1990). The exclusion criteria for CBT were: Developmental Disability; moderate or severe thought disorder (score of 5 or greater on PANSS item P2), and current significant substance misuse (e.g. problems with alcohol or drug use occurring weekly or more; Humeniuk, Rachel, Ali, Robert & World Health Organization [WHO], 2006).

Referrals were screened at a weekly intake meeting regarding program criteria. Discussions among the clinical team members then considered the referral request, and assigned clients into three broad groups: clozapine starts, CBT, or other (viz. medication optimization, physician second-opinion only, or nursing support). Program staff subsequently reviewed the pre-existing clinical record and met with the patient to conduct an unstructured assessment interview.

The chart review for this study paralleled the clinical intake process. Where the client was deemed by the clinical team as eligible for either clozapine or CBT, the first author and a trained research assistant then reviewed the clinical record for eligibility for the alternate treatment. In so doing, we identified clients who met inclusion and exclusion criteria for both treatments, and thus for eligibility in a randomized controlled trial.

For dually eligible clients, the chart was further reviewed for indications regarding the relative merits of the two treatments. Those indications had not been identified in advance, so they were neither systematically queried nor recorded in the chart. Nonetheless, a wide range of considerations regarding the relative merits were extracted, e.g. whether clients stated a clear preference for choice of treatments, their residential setting (to aid in medication compliance or to support CBT homework), extended leave status, geographic proximity to services, the extent of concomitant substance use or other co-morbid conditions, and work or family commitments.

5. Results

Of the 137 clients accepted to the service, 59% were male. The mean age was 42 years, with a range of 18–88 years. Diagnostically, 73 clients (53%) were identified as having schizophrenia, and 45 (33%) were schizo-affective. Nineteen others (14%) were diagnosed as Psychosis Not Otherwise Specified (NOS; n = 5), Bipolar (n = 6), Major Depressive Disorder (4), or other (n = 4). Culturally, 98 clients (71%) were of Caucasian origin, 14 (10%) from South-east Asian backgrounds, and 25 (18%) from Indo-Pakistani families.

Figure 1 shows that the large majority of clients referred to the program were accepted (135 of 137; 98.5%). Of those accepted, 36% were referred for initiation of clozapine, and 22% were referred for CBT. A total of 57 (42%) were referred for other services.

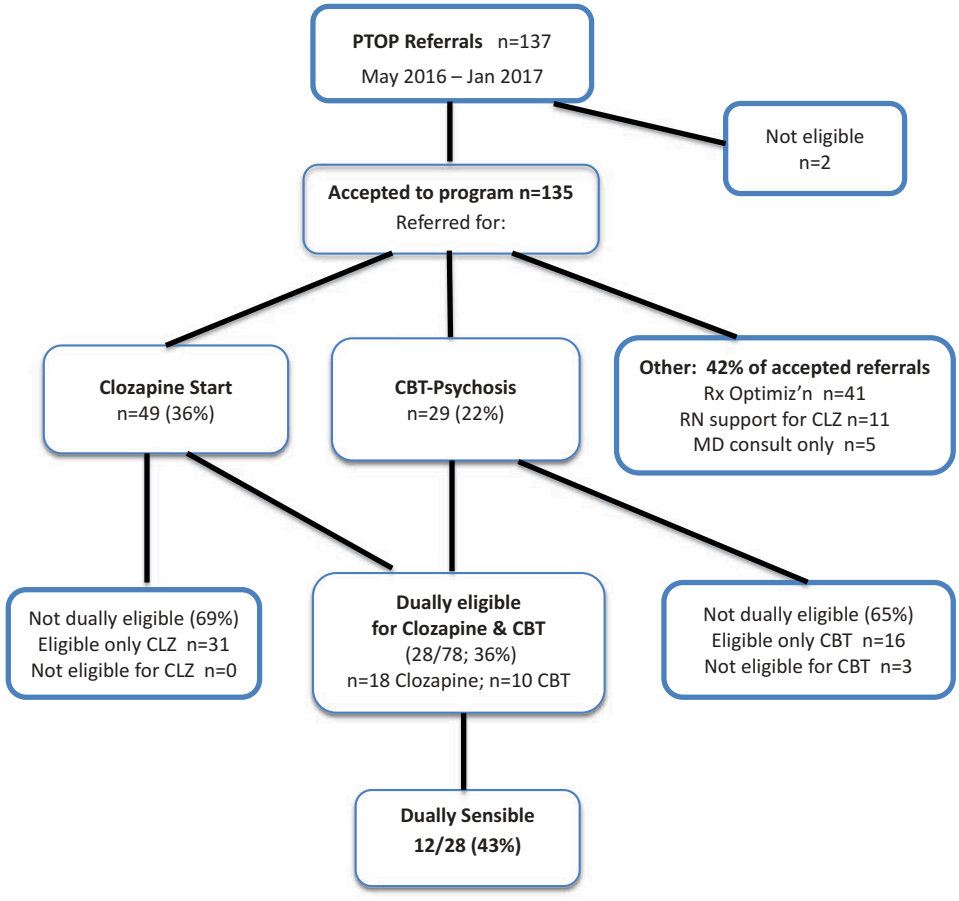
Approximately one-third of the patients referred for CBT or clozapine were deemed eligible for both treatments: 18 of 49 (37%) of clients referred for clozapine met criteria for CBT, and 10 of 29 (34%) referred for CBT met criteria for clozapine.

To consent to a randomized controlled trial, the treatments compared must both be clinically sensible. Here, the two treatments appeared equally sensible for 12 of the 28 (43%) dually eligible patients, or 9% of all clients accepted to this refractory psychosis program. Examples of clients who were dually eligible but not dually sensible include those who had: previously been on clozapine but were not interested in retitrating; minimal levels of insight; an independent lifestyle with a history of inconsistent medication compliance; already experienced substantial weight gain or problematic metabolic parameters; or family concerns.

6. Conclusion and discussion

A controlled trial of the relative efficacy of CBT and clozapine for refractory psychosis has not been published. This chart-review study would suggest that a head-to-head comparison of these two gold-standard treatments is indeed feasible: approximately one-third of clients referred for one of the two treatments would be eligible for both, and hence for randomization in a controlled trial. This preliminary conclusion is limited by the chart-review methods: a prospective feasibility study, or even a full controlled trial, is needed to assess its validity. If confirmed, the degree of overlap in

Figure 1. Feasibility results.



eligibility suggests that clinical services need the capacity for both treatments in order to meet national and regional guidelines.

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