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Preliminary communication

Depression treatment by withdrawal of short-term low-dose antipsychotic, a proof-of-concept randomized double-blind study

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ABSTRACT

Background and objective: Because increased dopamine neurotransmission occurs with most antidepressants, and because antipsychotics cause behavioural supersensitivity to dopamine, short-term low-dose antipsychotic treatment was tested on depressed patients with an expectation of clinical improvement in the supersensitive phase following drug withdrawal.

Method: This was a randomized, double-blind, placebo-controlled study of 48 patients who met criteria for DSM-IV® Major Depressive Disorder, were in a Major Depressive Episode, and had a Hamilton Depression Rating Scale (HAMD) rating of ≥ 14. Half the participants received 0.25 mg oral haloperidol each day for 7 days, after which they received placebo daily for 4 weeks. The other half received placebo throughout the trial.

Results: One week after stopping the medication, the HAMD ratings of the drug-treated patients fell by 9.96 points, as compared to a reduction of 8.73 points in the placebo-treated patients, when comparing visits 1 and 4. There was no such difference when comparing visits 2 and 4. The differences were not significant, but indicated a trend.

One week after the medication was stopped, the Clinical Global Index fell 1.64 ± 0.18 units for the medication-treated patients, compared to 1.12 ± 0.26 units for the placebo group ($P=0.05$). The regimen was well tolerated.

Conclusions: Seven days of an ultra-low dose of 0.25 mg haloperidol, followed by withdrawal of haloperidol, resulted in clinical depression improvement greater than placebo and significantly decreased psychomotor retardation, consistent with haloperidol-induced behavioural supersensitivity to dopamine.

Limitations: The sample was small. More patients are needed in a future study.

1. Introduction

Major Depressive Disorder (MDD) is one of the most prevalent mental health problems worldwide and brings with it considerable social and economic burdens. One person in five fulfills the Diagnostic and Statistical Manual of Mental Disorders (DSM IV[TR]) criteria for MDD over the course of a lifetime (Üstün et al., 2004). Although there is a considerable difference in the range of symptoms (persistent sadness, loss of self esteem, difficulty concentrating, guilt, hopelessness, avoiding other people, loss of appetite, loss of interest or pleasure, and suicidal thoughts) and in their severity, role functioning is usually affected adversely and the toll of disability is high. In 2000, MDD was the fourth leading cause of global disease burden, accounting for 4.4% of total disability-adjusted life-years (DALYs), causing the largest amount of non-fatal burden, and represents 12% of all total years lived with disability (Üstün et al., 2004). By 2020, it is predicted that MDD will be second among all diseases in the International Burden of Disease (Reddy, 2010).

The present study examines whether enhanced dopamine supersensitivity can quickly, if transiently, alleviate depressive symptoms. Most antidepressants take time to have therapeutic efficacy and need to be taken for at least one year and up to lifetime, depending upon risk factors for recurrence and patient preference (Suehs et al., 2008). They include compounds that inhibit the neural uptake of norepinephrine, serotonin, and dopamine, or

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stimulate the receptors for these neurotransmitters, but there are currently no strategies for enhancing the sensitivity of these receptors so that patients can respond more quickly and at lower doses.

The purpose of this study, therefore, was to enhance dopamine supersensitivity in patients by means of an ultra-low antipsychotic dose for a brief period (7 days) and then withdraw the drug in the expectation of a clinical improvement after drug withdrawal, when dopamine supersensitivity is known to occur (Seeman, 2011). The molecular mechanism underlying this type of post-antipsychotic supersensitivity is the induction of dopamine D2High receptors by the antipsychotic (Seeman, 2011). The dopamine D2 receptor is the major target of antipsychotic drugs. The D2 receptor can exist in either a state of high-affinity for dopamine, known as D2High, or in a state of low affinity for dopamine, known as D2Low. The D2High state is known to be the functional state of the D2 receptor (George et al., 1985).

It has been shown that treatment with antidepressant drugs (at normal antidepressant doses) produces a sensitization of behavioural responses to agonists acting at dopamine D2 receptors (so-called dopamine supersensitivity; Willner, 1997; Healy and McKeon, 2000; Spyraki and Fibiger, 1981; Kapur and Mann, 1992). Such a sensitizing action presumably assists in eliciting the clinical antidepressant effect. However, in contrast to the strategy of the present study, the antidepressant doses used in these earlier studies were maintained for relatively long periods of time.

Although the use of antipsychotics for depression has been controversial (Robertson and Trimble, 1982), the antidepressants amoxapine and trazodone appear to exert both antidepressant and antipsychotic effects (Apiquian et al., 2003). In addition, Robertson and Trimble (1982) have summarized studies showing that thioridazine, chlorpromazine, perphenazine, fluphenazine, thiothixene, flupenthixol, and chlorprothixene are as effective as imipramine, amitriptyline, or doxepin in treating depression, especially within the context of psychosis or schizophrenia. The doses of these antipsychotics for treating depression are generally lower than for psychosis. More recently, there have been reviews of low doses of the atypical antipsychotic amisulpride (50–100 mg/day) or levosulpiride (50–150 mg/day) used for dysthymia, a mild chronic form of depression (Pani and Gessa, 2002; Mucci et al., 1995). Blier (2013) has recently addressed the wider issue of using low dose atypical antipsychotics for depression.

However, the brief use of drugs that sensitize dopamine D2 receptors in order to effect a rapid, if transient, reversal of depression has not been previously described. The present study employed a short-term ultra-low-dose antipsychotic and sought to determine whether the subsequent rebound dopamine supersensitivity would be clinically beneficial in alleviating depressive symptoms.

2. Method

The study was approved by Health Canada as "A pilot placebo-controlled, double-blind, randomized parallel group study to evaluate the efficacy of treatment with CLR3001 in depression". Haloperidol (CLR3001) was given at a dose of 0.25 mg once per day orally in capsule form. The placebo, prepared commercially, was identical in shape and colour to the drug-containing pill. The protocol was approved by the Research Ethics Board of the University Health Network (Toronto, Ontario) where the study was conducted. At the beginning of the study, subjects were informed of the possibility of receiving a placebo at the start of the study. A series of 70 subjects (a sample size calculated to allow for drop-outs and to have sufficient power to reliably distinguish between 1 and 2 weeks after drug discontinuation in the two groups—80% at the $P=0.05$ level) was recruited by advertisement in newspapers and posters in Toronto, Ontario, Canada, as well as by physician referral. Participants were randomized after providing written consent. Inclusion criteria were: male or female outpatients aged 18 to 65 years meeting criteria for Major Depressive Disorder with a current Major Depressive Episode as per DSM-IV® and no more than 5 prior episodes. Patients had to be antidepressant-free for at least one week (28 days for prior fluoxetine and 14 days for prior irreversible monoamine oxidase inhibitors), not currently receiving psychotherapy, and able to provide written informed consent. The HAMD-17 score had to be ≥ 14 at both screening and at randomization visits. Patients had to be able to understand and complete questionnaires, and communicate with the study coordinator. Female participants of childbearing potential or those who were not at least 2 years postmenopausal or surgically sterile or totally abstinent or whose partner had a vasectomy needed to be using a reliable, medically acceptable form of contraception and agreeable to continuing such use throughout the duration of the study. Exclusion criteria were the following: investigators and immediate family members, treatment within the last 90 days with a drug that had not received regulatory approval at the time of study entry, lifetime diagnosis of bipolar disorder or any form of psychotic disorder, a primary diagnosis of panic disorder, generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, obsessive–compulsive disorder within the past year, the presence of an Axis II disorder, which, in the opinion of the investigator, would interfere with compliance in the study.

At screening, a medical history was recorded and laboratory tests (electrocardiogram, clinical chemistry, hematology and urinalysis) were completed. The Mini Neuropsychiatric Interview (MINI) was used to confirm MDD diagnosis and current MDE. At each visit, the patient was evaluated by a psychiatrist. The HAMD-17 rating scale was used to assess the severity of depression symptoms and the Clinical Global Impressions (CGI) scale was used to provide the clinician's general impression of the severity of the patient's condition. Because of the known ability of antipsychotics to induce behavioural dopamine supersensitivity and dopamine D2High receptors (Seeman et al., 2005), the psychomotor retardation item on HAMD-17 was identified a priori for individual item analysis. In addition, the Simpson Angus Scale (Simpson and Angus, 1970) was used to screen for extrapyramidal side effects at each study visit.

The protocol called for a total of 7 visits, where visit 1 was considered the screening visit and visit 2 served as the baseline visit, but both visits were used for a final analysis. The medication or the placebo was taken daily after the second visit until the third visit.

Forty-eight subjects completed the protocol to at least Visit 4, the week following discontinuation of the treatment, resulting in 26 control and 22 treated evaluable subjects. Reasons given for early drop out are shown in Fig. 1.

3. Results

3.1. HAMD-17 ratings

The placebo-treated patients ($N=26$) had an average HAMD-17 score of 21.69 ± 0.74 (mean $\pm$ s.e.) at visit 1, and 21.96 ± 0.75 at visit 2, before starting the placebo. At visit 4, the average HAMD-17 score was 12.96 ± 1.16, a reduction of 8.73 points from visit 1 and a reduction of 9.00 points from visit 2 (Table 1).

The drug-treated patients ($N=22$) had an average HAMD-17 score of 22.36 ± 0.8 (mean $\pm$ s.e.) at visit 1, and a rating of