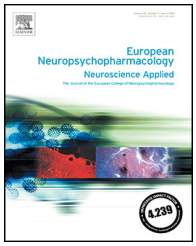
European Neuropsychopharmacology (2018) 000, 1–11



www.elsevier.com/locate/euroneuro

Dose reduction of high-dose first-generation antipsychotics or switch to ziprasidone in long-stay patients with schizophrenia: A 1-year double-blind randomized clinical trial

Jan P.A.M. Bogers[a,*], Peter F.J. Schulte[b], Theo G. Broekman[c], Peter Moleman[d], Lieuwe de Haan[e]

[a] *High Care Clinics, Mental Health Services Rivierduinen, Valklaan 3, Oegstgeest, 2342EB Leiden, The Netherlands*
[b] *Mental Health Services North-Holland North, Alkmaar, The Netherlands*
[c] *Bureau Beta, Nijmegen, The Netherlands*
[d] *Moleman Research and formerly Radboud University, Nijmegen, The Netherlands*
[e] *Academic Medical Centre, Amsterdam, The Netherlands*

Received 22 November 2017; received in revised form 5 June 2018; accepted 25 June 2018
Available online xxx

KEYWORDS
Antipsychotic agents;
Ziprasidone;
Schizophrenia;
Relapse;
Treatment failure;
Double-blind method

Abstract
Long-stay patients with severe schizophrenia are frequently treated with high doses of first-generation antipsychotics (FGA). Dose reduction or switching to ziprasidone may reduce the severity of negative symptoms and side effects.
We investigated in a randomized double-blind trial whether a dose-reduction strategy to achieve an adequate dose of a FGA (5 mg/day haloperidol equivalents, $n = 24$) or switching to ziprasidone (160 mg/day, $n = 24$) in treatment resistant patients would decrease negative symptoms after 1 year of treatment. We found that negative symptoms did not change significantly in either condition. Positive symptoms, excited symptoms, and emotional distress worsened over time with ziprasidone, resulting in a significant difference between conditions

* Corresponding author.
E-mail address: j.bogers@rivierduinen.nl (J.P.A.M. Bogers).

https://doi.org/10.1016/j.euroneuro.2018.06.005

Please cite this article as: J.P.A.M. Bogers et al., Dose reduction of high-dose first-generation antipsychotics or switch to ziprasidone in long-stay patients with schizophrenia: A 1-year double-blind randomized clinical trial, European Neuropsychopharmacology (2018), https://doi.org/10.1016/j.euroneuro.2018.06.005

in favour of FGA dose reduction. Relapse and treatment failure, defined as a prolonged or repeated relapse, occurred more often with ziprasidone than with FGA (45.8% versus 20.8%, and 25.0% versus 16.7%, respectively). Treatment with ziprasidone was superior for extrapyramidal symptoms.

Our study establishes that lowering high FGA doses to an equivalent of 5 mg/day haloperidol or switching to ziprasidone is feasible in the vast majority of patients but does not improve negative or other symptoms. Neither FGA dose reduction nor switching to ziprasidone is an adequate alternative to clozapine for long-stay patients with severe treatment resistant schizophrenia.

1. Introduction

Despite efforts to prevent chronic schizophrenia (Fusar-Poli et al., 2017) most patients still suffer from functional impairments that are associated with negative symptoms leaving a substantial proportion of patients with incomplete recovery and persistent illness (Sarker et al., 2015; Milan et al., 2016). Unfortunately, these patients are often treated with high doses or combinations of antipsychotics (Yamin and Vaddadi, 2010). High-dose antipsychotic therapy is associated with more and more-severe side effects, such as extrapyramidal symptoms, sedation, sexual dysfunction, sudden cardiac death, and possibly more substantial loss of brain tissue (Ray et al., 2009; Gallego et al., 2012; Andreasen et al., 2013). High doses are also related to subjective un-wellbeing and more-severe negative symptoms (De Haan et al., 2000; 2003; 2004). For this reason, dose reduction has been proposed repeatedly as part of the standard treatment protocol after a period of stabilization (Yamin and Vaddadi, 2010). Indeed, this strategy has been shown to have favourable effects on symptoms, well-being, social participation, and personal roles (e.g. Johnson et al., 1987; Hogarty et al., 1988; Kopelowicz and Liberman, 2003; Torrey et al., 2006). Although the benefits and risks of neuroleptic tapering are controversial (reviewed in Yamin and Vaddadi, 2010), a recent randomized study showed that dose reduction accompanied by switching from antipsychotic polypharmacy to monotherapy was well tolerated by almost 80% of patients (Borlido et al., 2016). Non-randomized open studies have shown dose reduction to be safe in patients receiving high-dose antipsychotics (Suzuki et al., 2003; Essock et al., 2011).

Another approach to diminish the severity of negative symptoms may be to switch to a second-generation antipsychotic (SGA). The development of these so-called "atypical" antipsychotics fuelled hope that switching to these medications might lead to better outcomes than with first-generation antipsychotics (FGA). Indeed a meta-analysis of the effectiveness of SGA versus FGA demonstrated SGA to be marginally superior to FGA for negative symptoms (Leucht et al., 2009a). Although the improvement in negative symptoms was statistically significant, it was not clinically meaningful (Fusar-Poli et al., 2015). Moreover, no specific SGA appeared to be superior concerning the treatment of negative symptoms (Leucht et al., 2009b). Nevertheless, some studies have shown ziprasidone to be more effective for negative symptoms than other antipsychotics in patients with chronic schizophrenia (Hirsch et al., 2002; Weiden et al., 2003; Kane et al., 2006; Olié et al., 2006; Samara et al., 2016). The unique pharmacological profile of ziprasidone may underlie its clinical effectiveness as a treatment for negative symptoms. Ziprasidone is a 5-HT_{1A} receptor agonist, an antagonist at 5-HT_{2A}, 5-HT_{2C} and 5-$HT_{1B/1D}$ receptors, and inhibits the neuronal uptake of 5-HT and norepinephrine (Schmidt et al., 2001).

The question remains what the optimal antipsychotic dose is to ameliorate or at least not aggravate negative symptoms. PET and SPECT studies have shown that therapeutic doses of antipsychotics occupy 60–80% of brain dopamine D2 receptors in patients (Seeman, 2010). Based on these studies and expert opinion, an equivalent of 5 mg/day haloperidol is considered by most experts as an adequate dose of antipsychotic in multi-episode or chronic patients (Buckley and Correll, 2008; Andreasen et al., 2010; Gardner et al., 2010; Yamin and Vaddadi, 2010), although Kreyenbuhl et al. (2010) have argued for higher doses. We hypothesized that dose reduction to a daily dose of 5 mg haloperidol equivalents may improve negative symptoms, without aggravating psychotic symptoms. Another strategy to reduce negative symptoms may be a switch to ziprasidone.

We investigated in a randomized double-blind trial whether a dose-reduction strategy to achieve an adequate dose of a FGA or switching to an equivalent dose of ziprasidone in treatment resistant, long-stay patients on relatively high doses of FGA would decrease negative symptoms after 1 year of treatment. Secondary outcomes were positive and disorganized symptoms, excitement and emotional distress, depressive symptoms, side effects, general functioning, relapse, and treatment failure.

2. Experimental procedures

2.1. Study design

This double-blind, randomized study with a follow-up of 1 year was conducted in 3 long-stay units of Rivierduinen Mental Health Organization in the Netherlands. In one condition ($n = 24$), the dose of the current FGA was reduced to 5 mg/day haloperidol equivalent, and in the other condition ($n = 24$) patients were switched to ziprasidone 160 mg/day, as 80 mg b.i.d., a dose considered equivalent to 5 mg haloperidol.

This study was part of a clinical research project investigating FGA dose reduction, ziprasidone (as SGA), and subsequently clozapine as treatment for severe schizophrenia.

Please cite this article as: J.P.A.M. Bogers et al., Dose reduction of high-dose first-generation antipsychotics or switch to ziprasidone in long-stay patients with schizophrenia: A 1-year double-blind randomized clinical trial, European Neuropsychopharmacology (2018), https://doi.org/10.1016/j.euroneuro.2018.06.005