

## Zuclopenthixol in adults with intellectual disabilities and aggressive behaviours

### Discontinuation study

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on behalf of the Zuclopenthixol Disruptive Behaviour Study Group

**Summary** We investigated the effects of zuclopenthixol on aggressive behaviour in patients with intellectual disabilities by randomly withdrawing it after a 6-week period of open treatment. Of the 49 patients responding to the treatment, 39 took part in a randomised withdrawal trial. The placebo subgroup ( $n=20$ ) showed more aggressive behaviour as indicated by outcomes observed by external raters on the Modified Overt Aggression Scale than did the continuing subgroup ( $n=19$ ). The results indicate that discontinuation of zuclopenthixol in this population leads to an increase in aggressive behaviour.

**Declaration of interest** T.G., M.B. and A.F.P. are employees of Bayer Vital GmbH.

People with intellectual disabilities are at higher risk of mental health problems compared with people from the general population. Particularly, people with intellectual disabilities show serious behavioural disturbances, such as disruptive and aggressive behaviour. Among institutionalised individuals with profound intellectual disabilities the incidence of self-injurious or aggressive behaviours ranges between 30 and 60% (Baumeister *et al*, 1998; Mikhail & King, 2001). Recent controlled studies of antipsychotic drugs focusing on risperidone reveal valuable effects on aggression and self-injurious behaviour in individuals with intellectual disabilities (Aman *et al*, 2002). However, risperidone produces adverse effects and is more expensive than conventional antipsychotic drugs which are rarely studied (Baumeister *et al*, 1998). To our knowledge, the study reported here is the first multicentre, double-blind placebo-controlled trial of zuclopenthixol

over the past 10 years involving adult patients with intellectual disabilities displaying severe aggressive behaviour.

### METHOD

A randomised, double-blind placebo-controlled withdrawal study for parallel groups was conducted in six German centres. Forty-nine people aged 18–50 years, with mild to moderate intellectual disabilities (IQ 30–70), received open treatment with zuclopenthixol for 6 weeks because of exacerbations of aggressive behaviour. Zuclopenthixol was administered at a dosage of 2–20 mg per day. The dosage was adjusted once or twice daily as judged necessary by the clinician. Eligible participants were mostly individuals in institutional settings who had complex behavioural problems as rated on the Disability Assessment Schedule (Holmes *et al*, 1982). All participants scored below 39 on this instrument. After complete description of the study to the participants and their legal representatives, voluntary written informed assent or consent was obtained from the participants or their legal guardians (or both) for participation in the investigation.

After open treatment, those in the responders group ( $n=39$ ) were randomised to continue or discontinue treatment for up to 12 weeks. Participants who discontinued treatment received placebo medication. Individual dosages were kept as stable as possible during the randomisation period. Concomitant use of other antipsychotics was not permitted throughout the study. Use of consistent doses of anticonvulsants as well as lithium, medication for extrapyramidal symptoms and benzodiazepines as an anti-epileptic escape medication was permitted. All concomitant medications were recorded. For all patients the Modified Overt Aggression Scale (MOAS; Yudofsky *et al*, 1986) was administered

every 2 weeks. Several secondary measures, medical history and safety measures, including possible withdrawal symptoms, extrapyramidal signs, vital signs and weight, were recorded. Routine laboratory tests of prolactin and serum levels of zuclopenthixol were conducted.

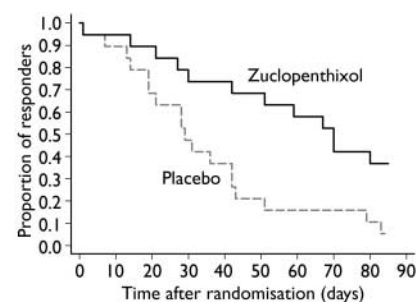
The primary efficacy measures were binary variables derived from weighted sums of the MOAS aggression sub-scores. The weighting of these scores gives a higher impact on severe (physical) forms of aggression (Kay *et al*, 1988). Patients with a deterioration of at least 3 points in MOAS sum scores at two subsequent visits when compared with their state at randomisation were designated as non-responders. All patients without deterioration were considered to be responders unless they withdrew from the study because of insufficient efficacy, concomitant treatment or adverse events.

Exclusion criteria were the presence of a diagnosed neurological disorder (without epilepsy), psychotic disorder, infantile cerebral palsy, hypersensitivity to zuclopenthixol and cardiac abnormalities. Female participants who were sexually active and did not use an effective form of birth control were also excluded.

### RESULTS

Results are reported here for the intention-to-treat sample only. The proportion of participants rated as responders, based on the weighted sum of MOAS scores 12 weeks after randomisation, was statistically significantly larger in the zuclopenthixol group (37%,  $n=7$ ) than in the placebo group (5%,  $n=1$ ); difference 32% (95% CI 3–61), Fisher's exact test  $P=0.020$ .

Figure 1 shows the Kaplan–Meier estimates of responder rates for the placebo group and for the zuclopenthixol group,



**Fig. 1** Kaplan–Meier estimates of responder rate based on the weighted sum of scores on the Modified Overt Aggression Scale.

log-rank test,  $P=0.005$ . Per protocol analysis yielded similar results.

Psychotropic adjunctive medications given after randomisation ( $n=7$ ) were equally distributed between the groups and involved the prescription of one benzodiazepine drug in each group. The number of adverse events and possible symptoms of withdrawal, such as nausea, insomnia, and diarrhoea, were recorded and did not differ between the groups.

## DISCUSSION

These results are in agreement with the studies of Singh & Owino (1992), who found zuclopenthixol to be more effective than placebo, and Malt *et al* (1995), who found zuclopenthixol to be superior to haloperidol in reducing unwanted behaviours. However, it should be noted that we used a discontinuation design in this study, and it was the withdrawal of zuclopenthixol that caused an increase in aggressive behaviour. In our study the beneficial effects of zuclopenthixol were found at low dosages between 6 and 18 mg (mean 11.4 mg). These dosages were lower than those in other studies in adults with intellectual disabilities and associated behavioural problems (Singh & Olwino, 1992; Malt *et al*, 1995). It is possible that these lower dosages might be responsible for the relatively high relapse rates in the continuation subgroup.

The anti-aggressive effects of zuclopenthixol may be explained by its

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dopaminergic mechanism, especially its high affinity to dopamine  $D_1$  receptors (Singh & Owino, 1992). Its high selectivity, together with the low dosages, may also explain the low rate of adverse effects. The psychopharmacological mechanism of zuclopenthixol differs slightly from the dopaminergic-serotonergic impact of risperidone; nevertheless, it provides a cost-effective alternative to the use of this atypical antipsychotic drug. Zuclopenthixol may be indicated especially in institutional settings, where patients and staff have to cope with severe forms of self-injurious and aggressive behaviours.

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