

Clozapine and weight gain

The information in this document is not intended as a definitive treatment strategy, but as a suggested approach for clinicians. It is based on previous successful experience. Each case should, of course, be considered individually.

This information is provided for healthcare professionals and should not be used as a patient information leaflet.

SmPC statement

The Summary of Product Characteristics (SmPC) for Clozaril[®] (clozapine)^{1,2} states that:

Weight gain has been observed with atypical antipsychotic use, including Clozaril[®]. Clinical monitoring of weight is recommended. Weight gain is listed as a common ($\geq 1/100$ to $< 1/10$) adverse reaction to Clozaril[®].^{1,2}

Background

Weight gain is a well-documented side effect of some atypical antipsychotics including clozapine. In addition, patients with schizophrenia are more likely to be overweight than the general population.³ Weight gain with clozapine is thought to be due to appetite stimulation with a multifactorial mechanism including effects on serotonergic, adrenergic and histaminergic neurotransmitter systems.⁴ It usually occurs during the first year of treatment.⁵

Gaining weight from antipsychotic treatment can have an influence on patient compliance⁶ and also gives added health risks such as an increase in the risk of hypertension, coronary heart disease and diabetes.

Prevention

The issue of weight gain should be discussed with the patient prior to starting clozapine. Motivational techniques, exercise and dietary counselling (before and during treatment) can be helpful preventative measures. Weight should be monitored routinely.

Management

The safest way for anyone to lose excess weight whether clozapine-related or not, is to use a combination of a low calorie diet accompanied by an increase in physical exercise. Referral to a dietician may be appropriate for some patients.

Orlistat, in conjunction with a mildly hypocaloric diet is licensed in the treatment of obese patients dependent on BMI and risk factors. It helps to lose weight by reducing the absorption of dietary fat and reducing the total calorie intake. There are some side effects associated with the use of orlistat especially if a high fat diet is consumed. Orlistat has been used to treat weight gain associated with antipsychotics, including clozapine.^{7,8} In a review article looking at the management of clozapine-associated weight gain, Whitney *et al* concluded that "Orlistat shows beneficial effects but in males only".⁹ However, Anghelescu *et al* reported 2 cases where female patients achieved weight reduction with a combination of diet, exercise and orlistat.⁸

A study by Hilger *et al* which looked at the effect of orlistat on the plasma levels of several different psychotropic drugs found no significant changes in the plasma levels of clozapine when orlistat was given although there were only 2 patients on clozapine.¹⁰ Orlistat has a very low systemic absorption but may impair the absorption of highly lipid-soluble drugs. Therefore, if a patient is to be treated with orlistat, consider checking the clozapine plasma level prior to starting it and monitor the patient for symptoms which could indicate a reduced clozapine plasma level.

Please refer to the relevant prescribing information for orlistat before prescribing the drug to patients receiving clozapine, available at <http://www.medicines.org.uk/emc> or <http://www.medicines.ie>.

Other drugs which have shown benefit in reducing clozapine-induced weight gain include aripiprazole, metformin and topiramate although the evidence supporting these drugs is limited.⁹

References

1. Clozaril (clozapine) Summary of Product Characteristics (online). Mylan Products Ltd. <<http://www.medicines.org.uk/emc/>> (Accessed on 02/04/2018).
2. Clozaril (clozapine) Summary of Product Characteristics (online). BGP Products Ireland Limited. <<http://www.medicines.ie/>> (Accessed on 02/04/2018).
3. Kurtzthaler I and Fleischhacker WW. The Clinical Implications of Weight Gain in Schizophrenia. *J Clin Psychiatry* 2001; **62** (suppl 7): 32-7.
4. Casey DE and Zorn SH. The Pharmacology of Weight Gain with Antipsychotics. *J Clin Psychiatry* 2001; **62** (suppl 7): 4-10.
5. Taylor D *et al*. The Maudsley Prescribing Guidelines in Psychiatry 12th Edition. Wiley-Blackwell. 2015.
6. Perkins DO. Adherence to Antipsychotic Medications. *J Clin Psychiatry* 1999; **60** (suppl 21).
7. Pavlovic ZM. Orlistat in the Treatment of Clozapine-Induced Hyperglycemia and Weight Gain. *European Psychiatry* 2005; **20**: 520.
8. Angheliescu I *et al*. Orlistat in the Treatment of Psychopharmacologically Induced Weight Gain. *Journal of Clinical Psychopharmacology* 2000; **20**: 716-717.
9. Whitney Z *et al*. Treatment of Clozapine-Associated Weight Gain: A systematic Review. *European Journal of Clinical Pharmacology* 2015; **71**: 389-401.
10. Hilger E *et al*. The Effect of Orlistat on Plasma Levels of Psychotropic Drugs in Patients With Long-term Psychopharmacotherapy. *Journal of Clinical Psychopharmacology* 2002; **22**: 68-70.

Adverse events should be reported.

For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

For Ireland, report adverse events via HPRA Pharmacovigilance medsafety@hpra.ie.

Adverse events should also be reported to Mylan via cpms@mylan.co.uk