Experience of thioridazine use before and after the Committee on Safety of Medicines warning

AIMS AND METHOD
To describe the use of thioridazine in a population of adults with learning disabilities at the time of the warning issued by the Committee on Safety of Medicines (CSM). Also, to observe the result of discontinuation of thioridazine and to examine factors that were associated with adverse events. Retrospective case note analysis was carried out for a sample of individuals with a learning disability.

RESULTS
Over 50% of those on regular thioridazine experienced adverse events during or following drug withdrawal. Adverse events were significantly associated with the duration of previous thioridazine prescription.

CLINICAL IMPLICATIONS
More caution may be required when reducing or withdrawing antipsychotic medication in this patient group.

Antipsychotic medication is commonly prescribed for individuals with learning disabilities. It is estimated that between 20% and 45% of this patient group are on such medication (Deb & Fraser, 1994). Management of behavioural problems appears to be the most common reason for the prescription of such drugs (Wressell et al, 1990). Psychiatric indications for antipsychotic drug prescription include: schizophrenia and other psychoses, mania, motor tics, severe anxiety and psychomotor agitation, excitement, agitation and restlessness, violent or dangerously impulsive behaviour and the control of deviant antisocial sexual behaviour (British Medical Association & Royal Pharmaceutical Society of Great Britain, 2001).

A recent, randomised controlled trial has shown that a substantial proportion of people with learning disabilities who were prescribed antipsychotic medication for behavioural disorders can now potentially have their drugs reduced or withdrawn (Ahmed et al, 2000). Worsening of behavioural problems, leading to drug reinstatement, has also been reported (Fielding et al, 1980; Briggs, 1989).

Thioridazine is an antipsychotic drug belonging to the phenothiazine group. Historically, within South Wales, it has commonly been prescribed among the group of patients with learning disabilities. On 12 December 2000, restricted indications and new warnings on the potential cardiotoxicity of thioridazine were circulated by the Chief Medical Officer and Chief Pharmaceutical Adviser of the National Assembly of Wales (Chief Medical Officer, 2000). The Committee on Safety of Medicines (CSM) had considered the evidence regarding prolongation of QTc interval and life-threatening ventricular arrhythmias observed with this drug. In summary, they advised that:

(a) thioridazine use should be restricted to the second-line treatment of schizophrenia in adults;
(b) the balance of risks and benefits is unfavourable for other previous indications;
(c) all patients should have a baseline electrocardiogram (ECG) and electrolytes, which should be repeated after a dose escalation and at 6-monthly intervals;
(d) thioridazine prescription should be re-evaluated and in cases of discontinuation, a gradual dose reduction over 1–2 weeks is recommended.

Following the CSM warning, a study was designed to describe the use of thioridazine in a population of adults with learning disabilities within Bro Morgannwg NHS Trust, South Wales. Other aims were to assess the effects of drug discontinuation and establish those factors that were linked to substantial problems in this patient group.

Method
The study was carried out within the Learning Disability Directorate of Bro Morgannwg NHS Trust, South Wales. (The Directorate provides services for a large catchment area, serving a population of approximately 1.3 million.) Individuals with a learning disability were identified who were known to community learning disability teams and/or consultant learning disability psychiatrists and who were prescribed thioridazine at the time of the CSM warning. A simple questionnaire was devised to assist in
Results

Of the 91 individuals included in the study, 77 were identified as being on regular thioridazine, the remaining 14 only taking it on an ‘as required’ basis. Of the 77 individuals on regular medication, the mean age was 45.5 years (standard deviation = 13.4 years, range = 16 – 81 years). Thirty-nine individuals were male and 38 female. The most common indications for prescription were for control of aggressive behaviour (n=27) and for management of symptoms of anxiety and/or agitation (n=23). Thioridazine was prescribed for other reasons in 18 individuals. These included psychoses, overactivity, restlessness, destructive behaviour, self-injury, mood disturbance and sleep disturbance. No clear indication could be found for the prescription of thioridazine in the remaining nine individuals. With respect to the degree of learning disability, 17 had a mild learning disability, 17 a moderate learning disability and 30 a severe or profound learning disability. Data were not available for the remaining 13 individuals. Forty-four individuals also had a psychiatric diagnosis, additional psychotropic drug prescription or immediate withdrawal of thioridazine. Although, on the whole, there is sparse literature on this subject, Branford (1996) found that the presence of epilepsy, lower initial antipsychotic dosage and a greater degree of learning disability were all associated with adverse events. Perhaps somewhat surprisingly, a number of individuals on very small doses (< 50 mg/day) had adverse events.

Discussion

This study demonstrates that over 50% of individuals with a learning disability who were taking thioridazine at the time of the CSM warning experienced significant problems during or after withdrawal, (albeit, eight of the individuals in the study group had a history of psychosis). Re-emergence of psychosis or mood disturbance was common, as well as escalation of behavioural disturbance. Tardive dyskinesia was observed in at least four individuals. The only finding that was significantly associated with adverse events was a longer total length of time on thioridazine. However, there were also trends that suggested that a severe/profound degree of learning disability, as well as a higher mean dose of thioridazine, might be factors related to a poorer outcome. Perhaps somewhat surprisingly, a number of individuals on very small doses (< 50 mg/day) had adverse events. Although, on the whole, there is sparse literature on this subject, Branford (1996) found that the presence of epilepsy, lower initial antipsychotic dosage and a greater degree of learning disability were all associated with better outcomes.

The rate of thioridazine withdrawal seemed less important than the actual amount by which the dose was

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<th>Box 1. Operational criteria to define ‘adverse events’</th>
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<td>During or following thioridazine drug withdrawal:</td>
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<td>(i) required admission/readmission to a psychiatric in-patient unit; and/or</td>
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<td>(ii) required an urgent domiciliary visit or out-patient appointment (including multi-disciplinary team involvement); and/or</td>
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<td>(iii) required alternative psychotropic drug prescription.</td>
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reduced. Although not statistically significant, the average weekly reductions of dose were 48 mg for the adverse events group (data available for n=19), versus 25 mg for the group who did not experience problems (n=11). Substitution of thioridazine with an alternative antipsychotic did not appear to affect outcome. The results here should be interpreted with caution as follow-up data were not complete for all individuals. However, for most analyses, results were available for at least 68 out of 77 individuals (88%), which is reasonable.

The findings suggest that special caution should be exercised when attempting to withdraw antipsychotic medication among individuals with a learning disability. Particular care should be exercised when withdrawing antipsychotics from individuals with a more severe degree of learning disability, those who are taking high doses and particularly those who have been on such medication for a long period of time.

**Declaration of interest**

None, other than that both authors were employed by Bro Morgannwg NHT Trust at the time the research was carried out.

**References**


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