

# Challenges Related to Thioridazine Use in Patients With Mental Retardation and Developmental Disabilities

Gerard Gallucci, M.D., MHS,<sup>1</sup> Daniel L. Buccino, MSW,<sup>1</sup>  
& Marie Cournoyer, MS, RN, CS-P<sup>1</sup>

<sup>1</sup>Community Psychiatry Program, Johns Hopkins Bayview Medical Center

Thioridazine has been widely used in the treatment of psychotic and non-psychotic disorders in patients with mental retardation and developmental disabilities. Recent labeling changes issued for thioridazine citing the drug's potential for fatal cardiac arrhythmia have necessitated a reconsideration of treatment regimens for patients maintained on thioridazine, some for many years. We report on two cases from our Special Needs Clinic for adults with psychiatric illness and mental subnormality or developmental disability. Most patients can be switched to other agents with good control of symptoms. However, some patients have been difficult to transition to newer medications. We present two different outcomes and offer clinical, theoretical, and pharmacological observations regarding the successes or challenges in transitioning from thioridazine to alternative medication regimens in this dually diagnosed population.

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The usefulness of dopamine antagonists for the treatment of both psychotic and non-psychotic disorders in individuals with mental retardation and developmental disabilities (MR/DD) has been well documented.<sup>1,5,9,10</sup> Thioridazine, in particular, has been widely used in this population for a variety of conditions and behaviors.<sup>6,8,15</sup> Thioridazine has been prescribed to treat psychotic disorders, including schizophrenia, affective illness and self-injurious behavior and aggression. Efficacy, in part, may relate to the sedative properties of the drug as well as its presumed primary mechanism of action involving the blockade of central dopamine receptors. While treatment with thioridazine has been limited by a significant number of adverse side effects,<sup>17</sup> this piperidine phenothiazine had remained a popular antipsychotic agent for the treatment of psychiatric illness in individuals with mental subnormality or developmental disabilities.

It has been reported that a number of psychotropic medications can be implicated in sudden death.<sup>12</sup> The polymorphic ventricular tachycardia, torsade de pointes, is characterized by prolonged QT. The mechanism and causes of this arrhythmia have been described.<sup>14</sup> Thioridazine appears to pose the greatest risk of torsade de pointes when compared with other antipsychotic drugs.<sup>7</sup> Recently, labeling changes

including a boxed warning were issued for thioridazine and related compounds that were found to prolong the QT interval.<sup>18</sup> The intent of the warning was to preclude the use of these agents in favor of compounds thought to be safer and possibly more effective. The labeling changes for thioridazine also indicated that the medication was not to be used with drugs that inhibit the cytochrome P450 2D6 isoenzyme or medications known to prolong the QTc interval. In addition, it was advised that patients with a history of cardiac arrhythmias or a congenital syndrome associated with a long QT should not be treated with thioridazine. Suggestions were made for EKG and serum potassium monitoring prior to and during treatment with thioridazine.

The Special Needs Clinic of the Johns Hopkins Bayview Medical Center provides comprehensive mental health services for adults with psychiatric illness and mental subnormality or developmental disabilities. These services include individual and group psychotherapy, family and careprovider support groups, case management and mobile outreach services, psychosocial and vocational rehabilitation, psychological and behavioral assessments, psychopharmacological evaluation and management, and coordination with other agencies and entitlements.

A substantial number of patients are treated with psychotropic medication, including typical and atypical antipsychotic medication for various diagnoses and behaviors. A group of patients had been treated with thioridazine for a number of years with good control of symptoms. We have been faced with the challenge of weighing the risk/benefits of thioridazine, recognizing the potential cardiotoxic effects of the drug, and have attempted to switch patients to possibly safer treatments. Results have been variable and some patients have been difficult to transition to the newer medications.

We describe two examples of patients attending the Special Needs Clinic who were previously treated with thioridazine and switched to an atypical agent with different outcomes. Clinical and theoretical observations regarding thioridazine use in patients with mental subnormality/developmental disability and a coexistent mental illness are discussed.

#### CASE A

Mr. A is a 25-year-old male with severe mental retardation, bipolar disorder and intermittent behavior problems. The patient also has a history of difficult-to-control seizures that began after an episode of herpes encephalitis at age 6. He has some spasticity but is ambulatory. He has limited verbal ability. He resides with his parents and attends a medical day program five days a week. In the program he requires a 1:1 staff person for intensive supervision and he receives activity and recreational therapy and assistance with activities of daily living.

Over the past several years his family reports he has shown some slight deterioration of cognitive, adaptive and physical functioning. Though the frequency and intensity of these episodes has remained stable over the past 15 years, his admission to the Special Needs Clinic was prompted by occasional episodes of aggressive behaviors, including hitting parents and staff at the day program, snapping his fingers, sleep disturbance, hyperactivity and running at home and at the day center. Behavioral interventions at home and in his medical day program did not produce significant reductions in problem behaviors.

The patient has been treated with a variety of medications for control of his seizure disorder and behavioral/mood problems. Past medications have included thioridazine, imipramine, lamotrigine, gabapentin, valproic acid, lorazepam and

quetiapine. His seizures are under fair control with adjustments of gabapentin and lamotrigine dosages. At time of admission to the Special Needs Clinic, the patient was being treated with gabapentin (1400mg t.i.d.), lamotrigine (150mg b.i.d.) and thioridazine (300mg). In the past, the patient's mother would give him PRN doses of thioridazine when he appeared more agitated and reported fair control and resolution of symptoms after receiving the additional doses of thioridazine.

After the patient was admitted to the Special Needs Clinic, a reduction in thioridazine dose was considered in conjunction with a trial of quetiapine for behavioral control and mood stabilization. The patient's mother was somewhat reluctant to discontinue the thioridazine and cited the usefulness of this medication during episodes of illness exacerbation. During the course of the thioridazine taper and quetiapine titration over a 6-month period, the patient had three episodes where he reportedly became more agitated and aggressive. His mother found PRN doses of thioridazine useful to control symptoms. The thioridazine dosage was eventually stabilized at 125mg/day PRN and the quetiapine dosage was titrated and is currently maintained at 125mg/day. The patient's mother has resisted any further reductions in the patient's thioridazine.

#### CASE B

Mr. B is a 20-year-old male with moderate mental retardation (full-scale IQ of 46 on WAIS-R), attention-deficit hyperactivity disorder, fetal alcohol syndrome and bipolar affective disorder who was admitted to the Special Needs Clinic for follow-up management of his psychiatric disorder after an inpatient hospitalization. There is a strong family history of bipolar affective disorder. The patient has documented exposure to alcohol in utero resulting in mild mental retardation and other stigmata of fetal alcohol syndrome. Neurological sequelae from prenatal alcohol exposure include mild left ptosis, mild left limitation of supralateral gaze, and mild visual impairment. Early speech and language evaluations identified severe receptive and expressive language deficits, which have impacted his academic performance and social relationships. The patient resides at home with his parents and brother. In addition to treatment and case management services in the Special Needs Clinic, the patient attends special education services and participates in a supported

vocational program where he has had success in several work placements.

Mr. B has been treated with numerous psychotropic medications and has experienced adverse effects from antipsychotics (haloperidol: extrapyramidal symptoms), lithium (toxicity), anticonvulsants (valproic acid and carbamazepine: bone marrow suppression), amphetamines (dextroamphetamine and methylphenidate: facial tics). When his outpatient care was transferred from our regular child and adolescent services, as he aged out of them, to the Special Needs Clinic, his medication regimen included thioridazine (37.5 mg/day), methylphenidate (20 mg/day) and diphenhydramine (50-100mg/day PRN for agitation).

After the black box warning and potential risk for sudden death from thioridazine, the patient's thioridazine was discontinued and chlorpromazine was started at 10mg b.i.d. The chlorpromazine dose was increased to 10mg. t.i.d. after the patient's mother reported the patient to be more agitated and hyperverbal. He subsequently developed worsening facial tics and chlorpromazine was discontinued and risperidone introduced at 0.25 mg/day with benztropine 1mg b.i.d. Risperidone was slowly increased to 1.5mg/day and benztropine titrated to 2mg/day to control complaints of mild stiffness. Methylphenidate was slowly tapered and discontinued.

The patient has tolerated this regimen well. His mood has been stable and there have been no significant behavioral problems noted at home or at school. He has been successful in his vocational and educational placements and works nearly full-time with some assistance from his job coach. He has been compliant with all aspects of his treatment plan.

## DISCUSSION

Historically, in addition to psychotherapeutic, behavioral, and case management services, antipsychotic medications have been widely prescribed for people with MR/DD. Thioridazine, in particular, was a frequently prescribed psychoactive agent for individuals with behavioral or psychiatric symptoms residing in institutions as well as in community settings.

The use of thioridazine in these populations appears to be declining. The recent warning that the potentially fatal arrhythmia, torsade de pointes, can be caused by the drug thioridazine is

one factor that has helped to shift the use from thioridazine to other medications for individuals with MR/DD who also experience a psychiatric illness. The more novel, atypical antipsychotic drugs have been shown to be more effective and safer than the older agents such as thioridazine although a number of adverse effects have been noted in this class of drugs, as well, including weight gain.<sup>13</sup> Cases of new-onset diabetes mellitus have been reported.<sup>2,19</sup> Other classes of medication such as antidepressants and anticonvulsants have proven to be useful for individuals with a dual diagnosis who had previously been treated with thioridazine. It should be recognized that these alternative drug therapies may carry a risk of cardiotoxicity. Tricyclic antidepressants are associated with orthostatic hypotension and pulse changes, QTc interval prolongation as well as other anticholinergic side effects. Adverse cardiovascular reactions from lithium include sinus node dysfunction, severe bradycardia and EKG changes. Arrhythmias and AV block have been reported with carbamazepine use.

In a population of outpatients attending a clinic for individuals with MR/DD and a major psychiatric illness, it has been our experience that most patients can be switched from thioridazine to another agent with good control of symptoms. In some cases, the recent FDA warning about the potentially dangerous cardiac complications from thioridazine and related compounds has helped us reassess the use of antipsychotic medication in certain patients and consider the use of other classes of psychoactive drugs to treat a variety of psychiatric conditions.

We have also recognized that some patients may be more difficult to switch from thioridazine to another agent. Several studies have highlighted the clinical outcome associated with the withdrawal from antipsychotic medication in patients with mental retardation or developmental disabilities.<sup>3,11</sup> A number of factors may account for this difficulty in changing to alternative medication. One factor may be that a rapid decrease in thioridazine would result in an anticholinergic withdrawal syndrome characterized by agitation, sleep disturbance and autonomic instability.<sup>4</sup> Behavioral deterioration following thioridazine withdrawal may result from adrenergic hyperactivity and be successfully treated with clonidine therapy.<sup>16</sup>

Another factor might be a perceived rather than actual benefit of the medication and a

reliance on the medication after many years of use. Case A illustrates how difficult it is to change medication regimens in the setting of intermittent exacerbations of illness, especially if the previous medication had an actual or perceived benefit for the patient. Even with consistent and intensive behavioral interventions, resistance to changing the medication from thioridazine to another agent was influenced by the apparent success of additional thioridazine to control symptoms or underdosing of an alternative agent. Since the taper of the original thioridazine dosage had been quite slow, it is unlikely that the agitation and hyperactivity experienced by Case A represented an anticholinergic withdrawal syndrome and was more consistent with an exacerbation of the patient's bipolar illness.

At the present time, patient A remains on a reduced thioridazine dosage in conjunction with an atypical agent and his anticonvulsant medication prescribed to control his seizure disorder. Periodic EKG and potassium monitoring will be obtained if the patient remains on thioridazine. In addition, adjustment of the quetiapine dosage will be considered and possible further taper of the thioridazine will be attempted. We will also consider use of lithium for mood stabilization. The patient's mother and day program providers were counseled not to use prn dosing of the thioridazine in view of the potential cardiac effects of the drug but to increase behavioral and environmental supports if symptoms recur.

Case B has been more typical of our experience in changing from thioridazine to another medication for an individual with MR/DD and a major psychiatric illness. He has successfully tapered off the thioridazine and tolerated the new medication without exacerbation of symptoms or adverse side effects. Compliance with the new medication, increased monitoring and agreement between the patient, his family and the treatment team regarding the goals for a safe and tolerable medication regimen contributed to the success of the medication changes.

In conclusion, it is our experience that most patients with MR/DD and a coexistent, major psychiatric illness can be successfully switched from thioridazine to other medication with good control of symptoms. Some patients, however, do appear to benefit from thioridazine and may not easily transition to alternative medication regimens, even with intensive behavioral

management programs. An awareness of the potentially dangerous cardiac complication from thioridazine makes ongoing monitoring and recognition of drug-drug interactions essential for those patients who remain on this psychotropic agent.

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Correspondence: Gerard Gallucci, M.D., MHS, Community Psychiatry Program, Johns Hopkins Bayview Medical Center, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 4940 Eastern Avenue, Suite D-2-East, Baltimore, MD 21224; tel.: 410-550-0088, fax: 410-550-1748, email: Ggallucc@jhmi.edu.