Late-onset Tay–Sachs disease: Adverse effects of medications and implications for treatment

Abstract—The authors conducted a retrospective and brief prospective study of adverse effects of approximately 350 medications in 44 adults with late-onset Tay–Sachs disease (LOTS). Some medications were relatively safe, whereas others, particularly haloperidol, risperidone, and chlorpromazine, were associated with neurologic worsening.

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Late-onset Tay–Sachs disease (LOTS) is an autosomal recessive lysosomal storage disorder caused by a partial deficiency of beta-hexosaminidase A (HEXA) activity, leading to the intracellular accumulation of gangliosides in the CNS. Manifestations include cerebellar, pyramidal, anterior horn cell, and cognitive dysfunction.[1-3] Psychiatric disturbance, including features of schizophrenia, depression, or bipolar disorder, occur in 30% to 50% of patients.[1-5]

Anecdotal clinical and laboratory reports suggest that psychotropic medications may worsen or accelerate neurologic symptoms in patients with LOTS,[4-6] including tricyclic antidepressants and antipsychotics including haloperidol and chlorpromazine.[6-9] We conducted a retrospective and prospective survey of medication effects in a cohort of 41 patients with LOTS.

Methods. After institutional review board approval, patients with LOTS were mailed a questionnaire containing a list of psychotropic and nonpsychotropic medications. With the aid of family and personal care assistants, patients identified medications they had taken, the period of time they were taken, and whether the medication had an adverse effect, no effect, or a beneficial effect on LOTS and other intended target symptoms. Specific adverse effects were recorded. Patients also kept a medication diary for 4 months, recording any worsening, improvement, or absence of change in their disease. Surveys were mailed to 44 patients (24 men), and diaries were mailed to 43 patients (23 men).

Returned surveys and diaries were followed up by a phone call from a physician investigator (S.H.-F. or B.E.S.). Patients were able to identify symptoms that began within days of starting a medication and remitted within days of discontinuing the medication, which we considered a side effect of a medication rather than exacerbation of the disease due to the medication. In addition, patients were able to distinguish between the slow, steady progression of their disease and a stepwise decline associated with medications. Symptoms associated with a combination of medications were noted. Patients' responses were confirmed by medical records if available. Neurologic worsening was defined as increased weakness, incoordination, imbalance, tremor, dysarthria, dystonia, cognitive decline, or worsening psychiatric symptoms. Medications taken by fewer than three patients were excluded, with the exception of tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressants, which were each grouped together. The small number of patients taking any one medication precluded formal statistical analyses.

Results. Forty-one patients responded, ranging in age from 23 to 79 years (mean age 39 years; mean age at diagnosis 29 years), and returned 38 surveys (22 men) and 27 diaries (13 men).

Retrospective survey. Psychotropic medications. Psychotropic medications are listed in table 1.

Antipsychotics. Antipsychotics most frequently associated with neurologic worsening included haloperidol (8 of 10 patients) and risperidone (5 of 6 patients). All 3 patients who took chlorpromazine reported neurologic worsening. Of 8 patients who took olanzapine, 3 worsened neurologically. Other antipsychotics are reviewed in table 1.

Antidepressants and electroconvulsive therapy. Of 6 patients who used tricyclic antidepressants, 1 reported psychiatric improvement without neurologic worsening (nortriptyline), and 1 reported psychiatric improvement with neurologic worsening (amitriptyline).

Of the SSRIs, only citalopram improved depression without neurologic worsening in any patient (2 of 2 patients). Three of 6 patients improved on paroxetine, whereas a fourth reported improved depression but increased weakness. Three of 9 patients improved while taking sertraline but worsened neurologically. Four of 7 patients improved while taking fluoxetine, 2 of whom worsened neurologically. Other antidepressants are reviewed in table 1.

Three patients underwent electroconvulsive therapy; 2 improved, 1 of whom worsened neurologically, whereas a third worsened neurologically without psychiatric improvement.

Mood stabilizers. Mood stabilizers that most frequently improved psychiatric symptoms without neurologic worsening included carbamazepine (9 of 13 patients) and lithium (5 of 11 patients), although 1 patient noted they only helped in combination. Another patient worsened neurologically while taking carbamazepine. Of 6 others treated with lithium, 3 worsened neurologically, 1 of whom reported psychiatric improvement. Of 8 patients exposed to valproic acid, 7 reported psychiatric improvement,

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Table 1 *Psychotropic medications reported by survey patients**

Psychotropic medications associated with neurologic worsening in some patients†		Psychotropic medications that improved target symptoms with no neurologic worsening in any patient‡	Psychotropic medications that improved target symptoms, some with neurologic worsening‡	
Antipsychotics	*Mood stabilizers*	*Psychotropics*	*Antipsychotics*	*Mood stabilizers*
Haloperidol (8/10)	Carbamazepine (1/13)	Nortriptyline (1/1)	Risperidone (2/6)	Carbamazepine (9/13)
Risperidone (5/6)	Lithium (3/11)	Citalopram (2/2)	Olanzapine (3/8)	Lithium (6/11)
Olanzapine (3/8)	Valproate (5/8)	Phenytoin (2/3)	Chlorpromazine (2/3)	Valproate (5/8)
Chlorpromazine (3/3)	Gabapentin (1/4)	Clonazepam (5/9)		Phenytoin (2/3)
	Lamotrigine (1/3)		*Antidepressants and ECT*	Lamotrigine (2/3)
			Nortriptyline (1/2)	Gabapentin (2/4)
Antidepressants and ECT	*Anxiolytics*		Amitriptyline (1/3)	
Amitriptyline (1/3)	Lorazepam (2/12)		Citalopram (2/2)	*Anxiolytics*
Paroxetine (1/6)	Diazepam (2/4)		Paroxetine (4/6)	Lorazepam (7/12)
Sertraline (3/9)	Alprazolam (1/4)		Sertraline (3/9)	Clonazepam (5/9)
Fluoxetine (2/7)			Fluoxetine (4/7)	Alprazolam (3/4)
Bupropion (2/4)	*Stimulants*		Mirtazapine (2/4)	
Mirtazapine (1/4)	Methylphenidate (2/4)		ECT (2/3)	*Stimulants*
ECT (2/3)				Methylphenidate (1/4)

* Medications listed were taken by more than 2 respondents. Patients not accounted for in the numbering either reported no effect or were not sure of the effect.
† Number of patients with neurologic worsening/number of patients exposed.
‡ Number of patients improved/number of patients exposed.

ECT = electroconvulsive therapy.

5 of whom worsened neurologically. The remainder of mood stabilizers are reviewed in table 1.

Benzodiazepines and other anxiolytics. Benzodiazepines that most commonly led to improvement were lorazepam (7 of 12 patients), clonazepam (5 of 9 patients), and alprazolam (3 of 4 patients). Two of 5 other patients who used lorazepam worsened neurologically. A fourth patient treated with alprazolam reported neurologic worsening at high doses. Of 4 patients treated with diazepam, 2 reported neurologic worsening.

Stimulants. Of 4 patients exposed to methylphenidate, 2 worsened neurologically and 1 reported improvement.

Nonpsychotropic medications. Table 2 lists general medications, supplements, and recreational drugs that improved target symptoms with no neurologic worsening. All 3 patients exposed to baclofen improved, 1 of whom worsened neurologically, whereas intermittent exposure to alcohol resulted in neurologic worsening in 2 of 6 patients.

Prospective diary. Of 27 diaries returned, 6 patients listed a total of seven medications not previously reported in their surveys. Only one medication, gabapentin, resulted in neurologic worsening in 1 patient, whereas the other patient tolerated it well.

Discussion. The data reported here confirm anecdotal reports of neurologic worsening in patients with LOTS treated with certain psychotropic medications, particularly haloperidol, chlorpromazine, and risperidone. Benzodiazepines were relatively safe and effective, in accord with anecdotal reports. Of the mood-stabilizing medications, carbamazepine was often effective in alleviating psychiatric symptoms, with the least frequent neurologic worsening.

Table 2 *General medications, supplements, and recreational drugs that improved target symptoms with no neurologic worsening in any patient*†*

Antibiotics	*Pain medications*
Clindamycin/ erythromycin (4/4)	Acetaminophen (Tylenol) (15/15)
	Ibuprofen (12/12)
Antihistamines/ sedatives	Naproxen (4/5)
Diphenhydramine (Benadryl) (10/12)	Acetylsalicylic acid (aspirin) (4/4)
Antacids/antidiarrheals	*Sleep aids*
Loperamide (Lomotil) (7/7)	Zolpidem (1/4)
Calcium carbonate (TUMS) (6/6)	Dextromethorphan/ acetaminophen/doxylamine/ pseudoephedrine (NyQuil) (1/4)
Bismuth subsalicylate (Pepto-Bismol) (5/5)	*Miscellaneous*
Magnesium hydroxide (Milk of Magnesia) (3/3)	Alendronate sodium (3/3)
Docusate (Colace) (3/3)	
Hormone replacement	
Ethinyl estradiol/ norethindrone (3/3)	

* Medications listed were reported by more than 2 respondents. Patients not accounted for in the numbering either reported no effect or were not sure of the effect.
† Number of patients improved/number of patients exposed.

Response to tricyclic antidepressants was clinically variable and inconclusive, perhaps because of the small sample size. Various nonpsychotropic medications were relatively safe and effective.

Because most of the psychotropic medications surveyed are lysosomotropic, amphiphilic weak base amines, the common denominator of the proposed mechanisms of CNS worsening is a further reduction of the already low level of residual intralysosomal HEXA activity that, in turn, results in additional pathologic accumulation of G_{M2} ganglioside. The pathogenesis of the drug effects likely involves multiple non–mutually exclusive processes including 1) increase of the intralysosomal pH, resulting in reduction of residual intralysosomal HEXA catalytic activity; 2) diminution of intracellular HEXA activity due to increased cellular secretion and impaired lysosomal enzyme receptor recycling; and 3) accumulation of multiple substrates within lysosomes that inhibit other lysosomal enzymes and are directly or indirectly cytotoxic.

For example, the tricyclic antidepressants have been shown in vitro to stimulate the secretion of lysosomal enzymes such as HEXA from cultured fibroblasts. These and other lysosomotropic agents, such as chlorpromazine and haloperidol, increase the intralysosomal pH, cause the secretion of other lysosomal enzymes, and cause a cellular lipidosis[6,8,9] or storage of other molecules such as glycosaminoglycans.[10] The intralysosomal storage of these molecules can also secondarily inhibit other lysosomal enzyme activities.

The retrospective nature of the study precluded determination of the precise doses or duration of the medications taken. Although patients may have been biased toward recalling medications associated with adverse effects, this would nevertheless tend to support the relative safety of other medications. Notwithstanding the limitations of a retrospective study, our data support reports of neurologic worsening in patients with LOTS exposed to certain psychotropic medications, notably haloperidol. Our data also implicate risperidone and chlorpromazine in neurologic worsening and support the use of lorazepam, clonazepam, and carbamazepine in patients with LOTS. Some general medications were also safe and effective.

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