Effects of Antidepressants on Longevity and Dementia Onset Among Adults With Down Syndrome: A Retrospective Study

John A. Tsiouris, MD; Paul J. Patti, MA; and Michael J. Flory, PhD

ABSTRACT

Objective: To investigate the effects of antidepressants on longevity, age at dementia onset, and survival after onset among adults with Down syndrome, controlling for late-onset seizures, trisomy 21 mosaicism, and cholinesterase inhibitor use.

Method: The charts of 357 adults with Down syndrome (mean age at first visit = 46.3 years, SD = 9.0) evaluated in a metropolitan diagnostic and research clinic between 1990 and 2008 were reviewed. Seventeen patients had trisomy 21 mosaicism; 155 patients were diagnosed with depressive disorders using *DSM-III-R* and *IV* criteria, 78 of whom received antidepressants for over 90 days. Of 160 patients who developed dementia, the estimated mean age at onset was 52.8 years. Fifty-six patients (demented and nondemented) had late-onset seizures. Longevity and age at estimated onset among those receiving and not receiving antidepressants were compared. Cox proportional hazards models examined risks for dementia onset and death.

Results: The mean age at dementia onset among those receiving antidepressants before onset was 53.75 years versus 52.44 years among others. Proportional hazards models showed a significant delay of onset among those taking antidepressants (hazard ratio = 0.69; 95% CI, 0.48–0.98; $P = .038$). Mean age at death or at end of study for those receiving antidepressants was 54.71 years; among others, it was 52.60 years (hazard ratio = 0.63; 95% CI, 0.42–0.94; $P = .024$). Among the 35 adults with late-onset seizures and dementia who died, mean survival after seizure onset was 4.23 years.

Conclusions: The findings in this retrospective study revealed that antidepressant use was associated with delayed dementia onset and increased longevity in adults with Down syndrome; mean survival after late-onset seizures was longer than previously reported. Further studies, however, are needed to confirm these associations, optimally in a clinical trial to confirm causality.

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Corresponding author: *Paul J. Patti, MA, George A. Jervis Clinic, NYS Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Rd, Staten Island, NY 10314 (paul.patti@opwdd.ny.gov).*

The life expectancy of people with intellectual disabilities has increased steadily over the last 80 years.[1–3] However, the life expectancy of people with Down syndrome is lower compared to people with intellectual disabilities from other etiologies.[4,5] This lower life expectancy is mainly due to the development of dementia, predominately Alzheimer's disease, in adults with Down syndrome, which has been reported to start around age 40 years in a few cases but increases steadily in prevalence after the age of 50.[6–8] The most important disorders related to mortality in adults with Down syndrome are dementia, epilepsy, mobility restrictions, and visual impairments but not cardiovascular diseases.[9] The survival period from the onset of dementia was reported to be 3.5 years for incident cases in institutionalized adults with Down syndrome and for people with more severe degrees of intellectual disabilities, while the mean age at death was 59.3 years.[10]

Factors such as depressive disorders (treated and untreated), late-onset seizures, and mosaicism, which can affect the onset of dementia and longevity in adults with Down syndrome, have not been investigated with good controls for potential confounders. Psychiatric disorders were diagnosed at higher frequencies in adults with Down syndrome above age 45 years,[11] and depressive disorders were the most common diagnoses.[12,13] It has been observed that depressive disorders and Alzheimer's disease have overlapping symptom presentation in adults with Down syndrome,[12,14–16] and their frequency among those with Alzheimer's disease was found to be double that of those without.[8] Although the role of depressive disorders in precipitating or enhancing the symptoms of Alzheimer's disease is not clear, there is evidence that antidepressant medications, especially selective serotonin reuptake inhibitors (SSRIs), can increase neurogenesis[17–19] and enhance cognitive[20] and physical recovery following stroke.[21]

Adult late-onset seizures in the absence of dementia are rare in people with Down syndrome.[22] Late-onset seizures were estimated to occur in more than 50% of adults with Down syndrome and Alzheimer's disease, and the average life expectancy after seizure onset was reported to be 1.5 years.[23] McCarron et al[24] reported that seizures were significantly more common in adults with Down syndrome and Alzheimer's disease (56%) than in those without Alzheimer's disease (11%), and seizure onset occurs significantly more often in adults with Down syndrome at the end stage of Alzheimer's disease (84%) than in those at mid-stage (34%). Lott et al[25] reported that there is a strong association of seizures with cognitive decline in adults with Down syndrome and Alzheimer's-type dementia.

Studies have reported that antiepileptic drugs can induce adverse cognitive effects.[26–29] It has also been reported that treatment of late-onset seizures with phenytoin in persons with Down syndrome and dementia can produce significant side effects even at therapeutic levels and may contribute to a decline in cognitive and adaptive skills in adults with Down syndrome[30] that can affect life expectancy.

Mosaicism (3 copies of chromosome 21 in some but not all cells) was reported in about 2%–4% of people with Down syndrome.[31–35] The

clinical characteristics of trisomy 21 mosaicism can be highly variable, ranging from a full Down syndrome presentation to an essentially normal phenotype without dysmorphic features.[31,36] A study that looked at population-based estimates of survival revealed better overall survival rates for children with mosaic Down syndrome than for children with nonmosaic Down syndrome.[35] Unfortunately, little is known about factors influencing the clinical outcome in adults with trisomy 21 mosaicism due to the small number of cases that are available for study.[33] There are only a few case reports in the literature of early onset dementia associated with mosaicism.[36–39] In the study by Coppus et al,[8] of 271 adults with Down syndrome aged ≥ 45 years who had complete cytogenetic testing, 1.4% were found to have mosaicism; however, others have reported an increased rate of mosaicism in Down syndrome adults aged ≥ 65 years.[40] Cases of trisomy 21 mosaicism without any clinical or neuropathologic signs of dementia have also been reported,[41] suggesting that there may be a delay of onset or even an absence of dementia, which would increase longevity in this subgroup of the Down syndrome population.

The current report presents the findings of a retrospective study wherein the authors sought to investigate effects of antidepressants on longevity, age at dementia onset, and survival after onset among adults with Down syndrome, controlling for late-onset seizures, trisomy 21 mosaicism, and cholinesterase inhibitor use.

Clinical Points

- Antidepressants (selective serotonin reuptake inhibitors) prescribed for over 90 days to adults with Down syndrome with depressive disorders were associated with delayed dementia onset and increased longevity compared to those adults with Down syndrome with and without depressive disorders who were not taking antidepressants.
- Antidepressant use may maintain overall functioning, delay cognitive deterioration, and preserve quality of life, possibly through increased neurogenesis.
- Mean survival after late-onset seizures in 31% of the Down syndrome study group with dementia was 4.23 years versus 1.5 years as previously reported and may be due to the avoidance of treatment with phenytoin.

METHOD

Sample

The study cohort comprised the case files of 357 adults with Down syndrome who were referred to a metropolitan diagnostic and research clinic between 1990 and 2008 for a comprehensive evaluation. The common presenting problems were a change in behavior, psychiatric signs/symptoms, and a reported decline in cognitive abilities or activities of daily living skills. The evaluation included (1) review of the psychosocial, psychological, behavioral, medical, and psychiatric records; (2) information obtained from family members and agency staff who accompanied the person; (3) observations, interaction, and mental status examination of the referred person; and (4) a series of cognitive tests and measures to assist in confirming or excluding a diagnosis of dementia. The specific procedures and assessment protocol used during the evaluation process have been described elsewhere.[16,42] A summary of the diagnostic procedures is provided in eAppendix 1 at PSYCHIATRIST.COM. Chromosome analysis was done for confirmation of trisomy 21 and trisomy 21 mosaicism when not available in the records. All patients were seen 1 or more times by the first 2 authors (J.A.T. and P.J.P., respectively). All psychiatric diagnoses were formulated by the first author (J.A.T.) following the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised,[43] and for those patients seen after 1994, the Fourth Edition[44] and Text Revision[45] criteria were applied. Five of 9 criteria are required to be present for a diagnosis of major depressive disorder. Six of 9 criteria are observable and can be used to diagnose major depressive disorders, even in individuals who are nonverbal and have profound/severe intellectual disabilities.[46] At the end of the initial evaluation and any follow-up visits, written recommendations for care and treatment with an antidepressant or other psychotropic medication(s) were made to the guardian/referring agency according to the findings and established diagnoses.

Detailed information about the timing of progressive stages of dementia was available for 140 of 160 patients eventually diagnosed with dementia. For those patients, the date of dementia onset was deemed to be the date on which the features of dementia were present for the diagnosis to be made. If a significant decline in functioning had already occurred, indicating a more severe stage of dementia prior to the first visit, an estimate of the date of onset was made using a rate of progression calculated from observed progression through stages among those patients for whom longitudinal staging information was available. If staging information was not available, the estimated date of onset was taken to be the date of first diagnosis. Of the 160 individuals eventually diagnosed with dementia, 74 were diagnosed on or within 30 days of the first clinic visit. Of those individuals, 41 (55%) were at the earliest stage of dementia. Of the 66 individuals diagnosed more than a month after the first visit, 53 (80%) were at the earliest stage of dementia when diagnosed.

The case file of each subject in the study cohort was reviewed, and data were transcribed to a specially designed form and then entered into a central database for analysis. Two undergraduate college students were trained and instructed on how to record and enter the data. They were not aware of the purpose of the study. Prior permission was obtained by the authors from the clinic's Institutional Review Board for retrieving data from clinic case files.

The characteristics and clinical information of the 357 adults with Down syndrome reviewed are presented in Table 1. Age at first visit ranged from 17 to 66 years (mean = 46.3 years, SD = 9.0), and 198 (55.5%) were men. Seventeen patients (4.8%) were found to have trisomy 21 mosaicism. Of the 309 patients with diagnostic information, 155 were diagnosed with depressive disorders (86% had major depressive disorder

and the remaining 14% had either dysthymic disorder or depressive disorder not otherwise specified). A total of 98 patients were prescribed antidepressants by their treating psychiatrist before or after they were seen in our clinic (98% were prescribed reuptake inhibitors, mostly SSRIs, and in a few cases, serotonin-norepinephrine reuptake inhibitors, and 2% were prescribed tricyclics/bupropion). In 20 patients, however, the antidepressant prescribed was discontinued within 90 days due to side effects or for other reasons by their guardians. For 57 of the 155 adults diagnosed with a depressive disorder, their guardian or treatment team did not follow the suggestion for treatment with an antidepressant. For the remaining 78 patients, antidepressants were prescribed for at least 90 or more days. Among 160 adults who were diagnosed with dementia (mostly Alzheimer's type) at the initial evaluation or at a follow-up visit, the estimated mean age at onset was 52.8 years (SD = 5.15); late-onset seizures (mostly tonic-clonic type) were diagnosed in 50 of these patients (see Table 1).

The diagnosis of late-onset seizures was first made by community neurologists (private offices, clinics, hospital emergency rooms) where the adults with Down syndrome were taken by their staff (or guardians) who observed seizure activity and was confirmed by the neurologists in our clinic. Laboratory tests (see Appendix 1) were done to rule out possible causes for seizures other than dementia. Electroencephalograms were done in all cases. Magnetic resonance imaging of the brain was done only when the person was cooperative and general anesthesia was not required or as directed by the primary neurologist.

Table 1. Characteristics of the Study Sample (N = 357 except as noted)

Characteristic	Study Sample
Male, n (%)	198 (55.5)
Age at first visit, mean (SD), range, y	46.3 (9.0), 17–66
Mosaicism, n (%)	17 (4.8)
Late-onset seizures (includes nondemented), n (%)	56 (15.7)
Among demented[a]	50 (31.3)
Among nondemented[b]	6 (3.0)
Dementia diagnosis by end of study, n (%)	160 (44.8)
Estimated age at onset of dementia, mean (SD), range, y[a]	52.8 (5.15), 39–67
Medication for dementia (includes nondemented), n (%)	118 (33.1)
Among demented[a]	100 (62.5)
Among nondemented[b]	17 (8.6)
Major depressive disorder, dysthymia, and/or depression not otherwise specified, n (%)	155 (43.4)
Antidepressants prescribed for treatment	98 (63.2)
Antidepressants prescribed for ≥ 90 d	78 (50.3)
Died by end of study, n (%)	105 (29.4)
Age at death, mean (SD), range, y[c]	55.1 (6.9), 36–67

[a]n = 160. [b]n = 197. [c]n = 105.

Analytic Methods

Longevity, age at dementia onset, and survival after dementia onset among those who took and did not take antidepressants for more than 90 days were compared using Cox proportional hazards models, a form of statistical survival analysis that examines factors influencing the time until an event (ie, dementia, death) occurs. Cox models assume that a factor has the same effect on the likelihood of an event at any point in time; the effect is expressed as a hazard ratio, a form of risk ratio.[47] Cox models also use the information from partially informative cases, in this instance, those who are still free of dementia or alive at the end of the study. In addition, Kaplan-Meier curves[48] were generated for each of these analyses and are presented in the figures following the analyses. Mosaicism, late-onset seizures, and use of cholinesterase inhibitors were controlled in these analyses.

RESULTS

The mean age at dementia onset among those who received antidepressants before onset was 53.75 years (SD = 5.17) versus 52.44 years (SD = 5.12) among those not taking antidepressants. A Cox regression controlled for potential confounders (mosaicism, late-onset seizures, and use of cholinesterase inhibitors) showed a significant delay of dementia onset (hazard ratio = 0.69, $\chi^2_1 = 4.31$, $P = .038$) (Table 2). The Kaplan-Meier survival curves in Figure 1 illustrate the difference in the proportion with and without dementia at each age among those who received and those who did not receive antidepressants.

The maximum age (age at death or at end of study) among those receiving antidepressants was 54.71 years (SD = 7.20) and 52.60 among the others (SD = 7.56). The Cox regression (in which age at the beginning of the study, mosaicism, late-onset seizures, and use of cholinesterase inhibitors were covaried) revealed that antidepressant use increased longevity (hazard ratio = 0.63, $\chi^2_1 = 5.12$, $P = .024$) (see Table 2). Figure 2 illustrates the difference in proportion surviving to each age among those who received and did not receive antidepressants.

The mean survival after the onset of dementia was 5.13 years (SD = 2.53) among those receiving antidepressants and

Table 2. Effects of Antidepressants on Estimated Age at Dementia Onset, Maximum Age Attained, and Survival After Dementia Onset[a]

	Took Antidepressants									
	Yes			No			Antidepressant Effect			
Variable	Mean	SD	95% CI	Mean	SD	95% CI	χ^2_1	*P*	Hazard Ratio	95% CI
Estimated age at onset of dementia, y	53.75	5.17	43.62–63.88	52.44	5.12	42.41–62.47	4.31	.038	0.69	0.48–0.98
Age at death or at end of study, y	54.71	7.20	40.60–68.82	52.60	7.56	37.78–67.42	5.12	.024	0.63	0.42–0.94
Survival after onset of dementia, y[b]	5.13	2.53	0.17–10.09	4.70	2.91	−1.68–9.72	0.89	.345	0.77	0.45–1.32

[a]Mosaicism, late-onset seizures, and use of cholinesterase inhibitors are included as covariates in all analyses. Effect sizes are net of their effect.
[b]Estimated age at onset of dementia is included as a covariate in this analysis, and the effect size is inclusive of its effect.

Figure 1. Effect of Antidepressant Use on Estimated Age at Dementia Onset or at End of Study

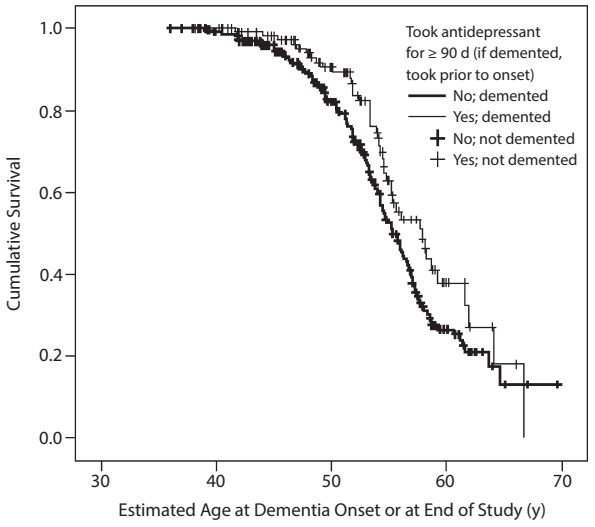


Figure 2. Effect of Antidepressant Use on Maximum Age Attained by End of Study

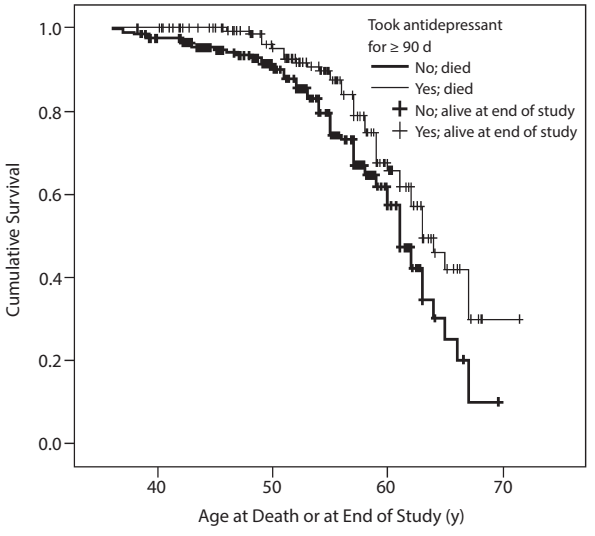
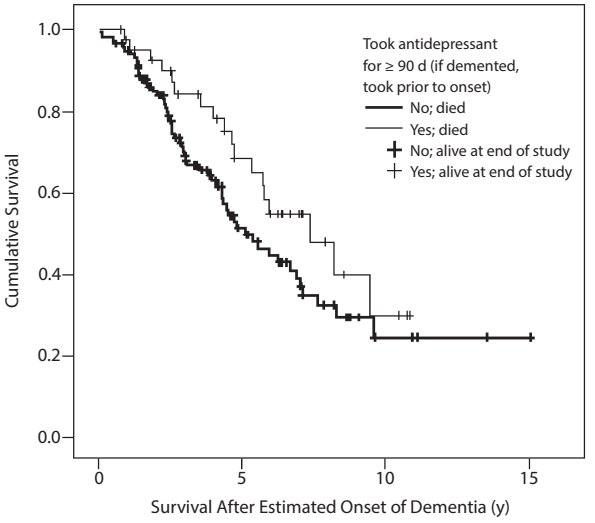


Figure 3. Effect of Antidepressant Use on Survival (proportion surviving)



4.70 years (SD = 2.91) among the others (see Table 2). While suggestive, the difference in survival was not statistically significant ($\chi^2_1 = 0.89$, $P = .345$). Figure 3 shows the difference in years of survival after dementia onset among those who received and did not receive antidepressant medications.

There were no statistical differences in sex, presence of mosaicism, or late-onset seizures between those receiving and not receiving an antidepressant for 90 days or more. Likewise, among those who received a dementia diagnosis, these factors did not differ significantly between those who did or did not take antidepressants prior to dementia, although disability level was more severe among those who did not receive antidepressants.

A significant difference ($P = .042$, Fisher exact test) was seen between rates of dementia among those receiving an antidepressant (80/157, 51%) and among others (80/200, 40%). Age at entry to the study was slightly higher ($F_1 = 4.68$, $P = .031$) among those receiving antidepressants (mean = 42.5 years, SD = 8.29) than among others (mean = 40.6 years, SD = 8.33). From the collected data, 62% (n = 100) of the 160 patients diagnosed with dementia were prescribed a cholinesterase inhibitor (mostly donepezil). Cholinesterase inhibitors were more likely to have been prescribed to those who received antidepressants (63/157, 40%) than to others (54/200, 27%) ($P = .009$, Fisher exact test).

Analyses did not reveal any group differences in the prevalence of 14 of 15 identified medical disorders in subjects' records (eg, diabetes, hypothyroidism, circulatory/heart problems, sensory deficits, etc), the sole exception being incontinence ($F_{348,1} = 7.40$; $P = .007$), which was more prevalent in the group taking antidepressants for more than 90 days. Of the 160 patients with dementia, 50 (31%) were reported to have experienced late-onset seizures; among the 35 of 36 who had died and for whom information was available, the mean duration from the onset of seizures to death was 4.23 years (SD = 3.70).

DISCUSSION

The findings in this retrospective study suggest that the use of antidepressants administered to adults with Down syndrome for 90 days or more was associated with a delay in the age at dementia onset and increased longevity. Further analyses revealed that there was no significant delay in dementia onset or longevity in the adults with Down syndrome with depressive disorders receiving versus those not receiving antidepressants. These findings may be explained by previous reports that SSRI antidepressants can enhance cognitive functioning[20] and physical recovery after stroke[21] due to increased neurogenesis in brain cells[17–19] and not to the reversal of depressive symptoms per se. However, we have observed in this study, as in a previous study,[16] an

improvement in sleep, appetite, energy levels, and interest in the environment and activities, along with elevation of mood and a decrease in behavior problems, in the group diagnosed with depressive disorders that was treated with antidepressants. The higher rate of incontinence present in the group receiving antidepressants may be explained by the fact that a higher percentage of adults with Down syndrome taking antidepressants were diagnosed with both depression and dementia; incontinence is a common symptom in middle- and late-stage dementia and in major depressive disorder in people with intellectual disabilities.

The clinical significance of the present findings suggests that antidepressants may sustain or even improve the quality of life in people with Down syndrome. Antidepressants can preserve their overall functioning by resolving the signs and symptoms of depressive disorder and preserve the length of intact cognitive functioning by delaying the onset of dementia.

In the present study, only 31% of 160 adults with Down syndrome diagnosed with dementia developed late-onset seizures. This finding represented a far smaller percentage than the 75% of cases reported by Prasher and Corbett[23] and the 56% of cases reported by McCarron et al.[24] Longevity after late-onset seizures was found to be 4.23 years versus 1.5 years as previously reported by Prasher and Corbett.[23] The difference between the present and the previous findings is possibly due to the differences in sample size and the population studied. The increased longevity in the study cohort after seizure onset can also be attributed to the fact that phenytoin was not used for the treatment of late-onset seizures in the cases studied but may have been used in some of the cases cited by Prasher and Corbett.[23] Even at therapeutic levels, phenytoin was found to cause a decline in mobility, cognition, and activities of daily living/self-care skills.[30] Health care professionals involved in the care and treatment of individuals with Down syndrome seen in our clinic were alerted about the authors' initial observations of the adverse effects of phenytoin when prescribed for late-onset seizures.

The practice of medicine for the past 20 years and especially the treatment of medical disorders in the population with intellectual disabilities are considered comparable in the United Kingdom and United States. This fact suggests that it is not better medical care but rather the replacement of phenytoin with other anticonvulsants that may have contributed to the increased longevity in our cohort. Future studies with older adults with Down syndrome or intellectual disabilities and dementia (both prospective and population-based) will help to clarify the issue of the prevalence of late-onset seizures during dementia and its effect on longevity, controlling for the choice of anticonvulsant medication and other variables.

The age at onset of dementia was later (mean age of 56.10 years) for those individuals with trisomy 21 mosaicism than for those without mosaicism (mean age of 52.08 years). This result supports the preliminary findings of Zigman et al[40] and Schupf and Sergievsky.[41] Of the 357 adults with Down syndrome in the study cohort, 17 (5%) were documented to have mosaicism, a slightly higher number compared to the expected 2%–4% (7–14 cases). One explanation is the random biased sample of patients with behavior problems, signs/symptoms of depression, and probable dementia who were referred to our clinic for a diagnostic evaluation. Another explanation, which goes along with the observations made by Zigman et al,[40] is that the attrition rate in younger and middle age adults is higher in nonmosaic than in mosaic cases, leading to a higher percentage of mosaicism in older adults with Down syndrome.

The results also revealed that a higher percentage of those who received antidepressants were also prescribed cholinesterase inhibitors. It was speculated that the delay of dementia onset cannot be attributed to the use of cholinesterase inhibitors because they typically were prescribed after the diagnosis of dementia. The data revealed that there were higher rates of dementia in the group receiving antidepressants, and only one-third of those prescribed cholinesterase inhibitors continued taking them for more than 2 months.

A variable that could have had an effect on the onset of dementia and survival/longevity was the apolipoprotein E genotype (ApoE). The presence of the ApoE ε4 allele was found to be associated with not only an increased risk of Alzheimer's dementia in people with Down syndrome but also with an increased risk of mortality.[9,49] Unfortunately, the ApoE status was not available for all of the subjects in the present study cohort, so a detailed analysis could not be completed. However, given the low frequencies of ApoE ε4 in the general population (7.1%–24%) (see Saunders et al[50]) and the fact that few of the documented cases in our cohort possessed the paired ApoE ε4/4 allele, this variable would likely not have affected the current findings.

The present study has a number of limitations in that it was retrospective in nature, and the study cohort was selected from a tertiary clinic population. As a result, one may not be able to generalize the present findings to the whole population of older adults with Down syndrome. Three hypotheses were tested in this study: first, that antidepressant use would delay dementia onset in adults with Down syndrome; second, that antidepressant use would extend longevity in this group; and, third, that antidepressant use would extend survival after the onset of dementia. Each of these hypotheses was tested with one statistical model, and, therefore, no adjustment for multiple comparisons was applied. The chance of Type I error for each hypothesis tested, therefore, is .05, the significance criterion that was applied.

The dosages of prescribed antidepressants were also not taken into account nor were subjects' residency or the stage of dementia when antidepressants were first prescribed. Another limitation is that psychotropics other than antidepressants and medications prescribed for medical disorders were not considered in the analyses. The possible positive effects of SSRI antidepressants on neurogenesis and delay of dementia onset in adults with Down syndrome deserves further investigation. More studies, prospective

in nature, are needed that explore these issues and, if done, should help to provide more insight into the delivery of better care and treatment for adults with Down syndrome with depressive disorders, dementia, and late-onset seizures.

CONCLUSIONS

The present retrospective study showed an association between use of antidepressants, delayed onset of dementia, and increased longevity in a group of adults with Down syndrome. The findings also revealed that the incidence of late-onset seizures in Down syndrome adults with dementia was lower and their survival after the onset of seizures was longer than previously reported. Further studies are needed to confirm these associations, optimally in a clinical trial to confirm causality.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), donepezil (Aricept and others), phenytoin (Dilantin, Phenytek, and others).
Author affiliations: George A. Jervis Clinic (Dr Tsiouris and Mr Patti) and Laboratory of Research Design and Analysis (Dr Flory), NYS Institute for Basic Research in Developmental Disabilities (NYS-IBRDD), Staten Island, New York.
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Supplementary Material

Article Title: Effects of Antidepressants on Longevity and Dementia Onset Among Adults With Down Syndrome: A Retrospective Study

Author(s): John A. Tsiouris, MD; Paul J. Patti, MA; and Michael J. Flory, PhD

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List of Supplementary Material for the article

1. Appendix 1
2.
3.
4.
5.
6.
7.
8.

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1

The following examinations, procedures, and tests were performed to rule out any other pathology or medical disorder that may be causing the reported decline, and to reach a diagnosis:

1. Physical and neurological examination performed by clinic neurologists.
2. An initial or repeat electroencephalography (EEG).
3. Blood work that included CBC, SMA-18, thyroid function tests, B_{12} and folate as well as cytogenetic testing to confirm a diagnosis of Down syndrome (if not previously performed).
4. Psychiatric examination using DSM III-R and DSM IV criteria.
5. The following cognitive tests (when appropriate) were performed on one or more occasions to assess memory-recall, psychomotor skills and adaptive functioning:
    a. ***Dalton/McMurray Visual Memory Test*** [1] – tests visual recognition memory functions using colored and simple pattern stimuli following a match to sample acquisition and delayed match to sample retention procedure
    b. ***Name Face Recall Task*** [2,3] – a visual-recall task that measures learning acquisition; assesses a person's ability to recall names and faces during four recall test trials

c. ***What's in the Bag****?* [3,4] - the person is asked to name and recall three common objects (*cup, ball, comb*) that are successively hidden in a bag. Three distracter objects (*key, spoon, scissors*) are used during the learning and acquisition trials.

d. ***Dyspraxia Scale for Adults with Down Syndrome*** [5,6,7] – taps the abilities to perform simple sequences of highly-practiced voluntary movements involved in the skills of daily living

e. ***Multi-Dimensional Observation Scale for Elderly Subjects (MOSES) Adapted for Persons with Down Syndrome*** [8,9,10] - a 40-item questionnaire that measures five areas of function: self-help skills, disorientation, depression, irritability, and social withdrawal

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