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ARTICLE

Serotonergic antidepressant effects on aggressive, self-injurious and destructive/disruptive behaviours in intellectually disabled adults: a retrospective, open-label, naturalistic trial

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Abstract

There is a growing body of evidence that serotonergic antidepressants are useful in the treatment of maladaptive behaviours in the intellectually disabled. However, not all studies have shown positive results due to lack of efficacy, tolerance development, and troublesome side-effects. The current study consisted of a review of the treatment response to a variety of serotonergic antidepressants, consisting of selective serotonin reuptake inhibitors (SSRIs) ($n=36$) and clomipramine ($n=2$) in 38 institutionalized intellectually disabled adults (20 males, 18 females; mean age 45.6 yr, age range 18–74 yr). Those studied were treated for aggression, self-injurious behaviours, destructive/disruptive behaviours, depression/dysphoria, or a combination of these or other challenging behaviours. Most were receiving concurrent psychotropic and/or anticonvulsant medications. Effectiveness was determined by a retrospective review of the summaries of multidisciplinary Neuropsychiatric Behavioural Reviews (NBRs) in which global and specific maladaptive behaviours were rated on a 1- to 7-point scale, and by psychologists' ratings of target behaviours. Overall, statistically significant decreases in the ratings of global maladaptive behaviour and aggression, self-injurious behaviour, destruction/disruption and depression/dysphoria and in psychologists' ratings occurred in the subject group after the initiation of antidepressants. The results suggest that serotonergic antidepressants are useful in the treatment of challenging/maladaptive behaviours in the intellectually disabled.

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Introduction

Intellectual disability is frequently associated with aggression towards self, aggression towards others, and/or destructive/disruptive behaviours (Baumeister et al., 1998). Such behaviours occur with increasing frequency as IQ decreases. Typical or conventional antipsychotic drugs have traditionally been the front-line treatment for these challenging behaviours (Baumeister et al., 1998), and newer 'atypical' antipsychotic agents have more recently been used (Aman, 1999; Cohen and Underwood, 1994; Horrigan et al., 1997, Janowsky et al., 2003; Lott et al., 1996; Martin et al., 1999; McCracken et al., 2002). However, advances in the diagnosis of mood and anxiety disorders, and an awareness of the limitations and dangers of utilizing conventional and atypical antipsychotic agents have resulted in a narrowing of the use of antipsychotic drugs to treat challenging behaviours.

A number of publications have supported the possibility that maladaptive behaviours in the intellectually disabled may be attenuated or alleviated by the administration of serotonergic antidepressant agents. Such agents include the selective serotonin reuptake inhibitors (SSRIs) and the serotonergic tricyclic antidepressant, clomipramine. The rationale for the

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use of these agents is, in part, that they are effective in the treatment of depression, anxiety and obsessive–compulsive disorder in non-intellectually disabled populations, and thus, may be useful in the intellectually disabled with similar disorders. Significantly, the above psychiatric disorders may manifest themselves as stereotypic, self-injurious, aggressive and disruptive/destructive behaviours in the intellectually disabled.

Previously, Gordon et al. (1993) observed that the selective serotonergic tricyclic antidepressant clomipramine was superior both to placebo and to the non-serotonergic antidepressant, desipramine in treating autistic behaviour in 30 subjects aged between 6 and 23 yr. Target behaviours included stereotypic, angry, compulsive and ritualized behaviours. Similarly, Lewis et al. (1995, 1996) studied the effects of clomipramine treatment on self-injurious behaviour (SIB) in studies of 10 and 8 adults respectively with severe mental retardation, using a double-blind, placebo-controlled design. These authors observed that clomipramine treatment was associated with improvement in the intensity of SIB, the frequency of stereotypy and compulsions, and a decrease in staff-reported interventions for problem behaviours. Garber et al. (1992) demonstrated that clomipramine was effective in decreasing chronic stereotypic and SIB such as head banging, head and face slapping, arm biting, eye gouging, aggression and tantrums in 10 out of 11 adolescents with developmental disorders. In a prospective open trial of clomipramine, Brodkin et al. (1997) observed that 55% of the 33 adults with Pervasive Developmental Disorder who completed the 12-wk trial were treatment responders, with clomipramine reducing repetitive thoughts and behaviours, aggression and improving social responsiveness.

With respect to the SSRIs, Bodfish and Madison (1993) reported improvement following fluoxetine administration of such symptoms as SIB and aggression in 7 out of 10 mentally retarded adults with compulsive disorders (and none of a group of comparison subjects without compulsive disorder). Similarly, Markowitz (1992) reported on the effects of an open trial of fluoxetine in alleviating aggression and SIB in 21 people who were severely or profoundly mentally retarded, and found improvement in all but two individuals, with marked improvement occurring in 13. Consistent with the above results, Fatemi et al. (1998) reviewed the charts of seven young adults with autistic disorder treated with fluoxetine. These authors found improvement in irritability, lethargy and stereotypy. Similarly, McDougle et al. (1996) observed that fluvoxamine treatment of 15 autistics was significantly superior to placebo in reducing repetitive thoughts and behaviours, maladaptive behaviours, aggression and in improving social behaviour and language usage.

In spite of the largely positive results outlined above, several studies of serotonergic-enhancing drugs in autistic and in other intellectually disabled people have not yielded such promising results. Varley and Holm (1990) found that tolerance to the serotonergic agent fenfluramine developed in six children with autism. Davanzo et al. (1998), studying SIB (i.e. head banging, biting self, hitting self, choking self, pulling one's hair) and aggression in 15 institutionalized people with mental retardation found that paroxetine only decreased aggression severity early in a 4-month trial. SIB diminished qualitatively at 1 month and increased above baseline as time passed. Similar tolerance to or decreasing effectiveness of SSRIs or clomipramine was noted in persons with Lesch–Nyhan Syndrome (Nyhan et al., 1980) and Prader–Willi Syndrome (Dech and Budow, 1991), and in cases of non-specific mental retardation (Ricketts et al., 1993). Branford et al. (1998), in a retrospective case analysis of 37 adults with intellectual disability who received fluoxetine or paroxetine, found that these SSRIs proved of no benefit in 40%, and led to deterioration in 25%. Thirty-five per cent showed some reduction in maladaptive behaviours. Similarly, Ghazuiddin et al. (1991) noted that SSRI antidepressants, while alleviating depression, did not seem to effect compulsive movements and stereotypy.

Finally, a consistent problem noted in many studies was the development of side-effects such as seizures, tachycardia, sedation, agitation, obvious worsening of target symptoms, constipation, irritability, decreased appetite, increased appetite, and sweating. As many as one third receiving serotonergic antidepressants developed such side-effects, often necessitating drug discontinuation (Branford et al., 1998; Davanzo et al., 1998; Lewis et al., 1995; McDougle et al., 1996; Sanchez et al., 1996).

In the current study, we retrospectively evaluated the effectiveness of a variety of serotonin-enhancing antidepressant drugs (serotonergic antidepressants) including paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram and clomipramine as treatments for maladaptive target behaviours in severely intellectually disabled institutionalized adults. Many of those studied were diagnosed as having bipolar and other mood disorders, obsessive–compulsive disorder, autism or impulsive disorders, all of which have been proposed at one time or another to be caused by abnormal serotonin activity.

Methods

Subjects

Those studied were 38 intellectually disabled adults who received treatment with a serotonergic antidepressant for behavioural purposes. They all were institutionalized at the Murdoch Center in Butner, North Carolina, a 580-bed state facility for the treatment of the intellectually disabled where they had resided from years to decades. They were a subgroup of a larger group of 225 Murdoch Center residents treated with one or more psychotropic agents for behavioural purposes (with or without serotonergic antidepressants administered) between 1994 and 2000.

To be included in the analysis, the subjects were required to have had an antidepressant free baseline evaluation [see Neuropsychiatric Behavioural Reviews (NBRs) below] and a subsequent evaluation following serotonergic antidepressant administration for at least 6 wk. Other subjects also received serotonergic antidepressants, but did not meet the above criteria (i.e. some arrived at Murdoch Center already receiving serotonergic antidepressants) and they were not included in the analysis.

The maladaptive behaviours treated included aggression towards others (i.e. hitting, biting, kicking, shoving, making aggressive threats, etc.), SIB (i.e. self-hitting, biting, head banging, cutting on one's skin, skin picking, skin scratching, etc.), destructive behaviours (i.e. overturning or breaking furniture, breaking windows, etc.), disruptive behaviours (i.e. screaming, yelling, uncontrollable running, tantrums, inappropriate stripping), other behaviours (i.e. masturbation, rectal digging, crying, whining, agitation, non-participation, non-compliance) or combinations of the above such behaviours. Those studied had been treated with an SSRI or clomipramine. The shortest period was 6 wk. All had a documented record of one or more maladaptive target behaviours prior to the initiation of the serotonergic antidepressant. There were no specific exclusion criteria.

The characteristics of the 38 adults studied are listed in Table 1. Subjects consisted of 20 males and 18 females. Their mean age was 45.6 yr, with an age range of 18–74 yr. Twenty-seven were Caucasian and 11 were African American. Over the years most had been assigned psychiatric diagnoses (generally made utilizing DSM-III-R or DSM-IV descriptions) based on clinical evaluations and psychiatric symptoms listed in the subjects' charts. These included Bipolar Affective Disorder, Major Depressive Disorder, Mood Disorder – NOS, Autism, Schizophrenia, Behavioural Disorder – NOS, and Conduct Disorder. All individuals studied had co-existing medical disorders and 19 had a seizure disorder. Twenty-eight had been evaluated as having profound cognitive intellectual disability, six tested in the severe range and four tested in the moderate range. Thirty showed profound, six showed severe,

Table 1. Diagnostic and demographic data on 38 intellectually disabled institutionalized adults receiving serotonergic antidepressants

Case no.	Age (yr), race, gender	Diagnosis
1	30, AA, Male	BPAD, Dep
2	68, AA, Female	Behav Dis
3	36, W, Male	Autism
4	30, W, Male	Autism
5	50, W, Male	Autism
6	36, AA, Female	Schiz
7	22, W, Male	Behav Dis, Autism
8	32, W, Female	No diagnosis
9	54, W, Male	Autism
10	47, W, Male	BPAD
11	33, AA, Female	Dep
12	49, AA, Female	No diagnosis
13	52, AA, Male	Behav Dis, Schiz
14	45, W, Female	BPAD
15	22, AA, Male	Explosive Dis
16	52, W, Female	BPAD
17	18, W, Male	Autism
18	71, W, Female	Conduct Dis
19	74, W, Female	Mood Dis
20	36, AA, Male	Dep, Disrup Dis
21	42, W, Female	BPAD
22	35, W, Male	Behav Dis
23	72, AA, Female	BPAD, Behav Dis
24	45, W, Female	OCD, Schiz
25	79, W, Female	OCD, Autism
26	57, W, Male	Language Dis
27	50, W, Male	OCD, Schiz
28	56, W, Female	Affective Dis
29	70, W, Female	BPAD
30	48, W, Male	Major Dep
31	50, AA, Male	No diagnosis
32	42, W, Female	Dep
33	24, W, Male	Behav Dis
34	33, W, Female	OCD, Autism, BPAD
35	53, W, Female	Behav Dis
36	35, AA, Male	Mood Dis NOS
37	52, W, Male	Personality Dis
38	43, W, Female	BPAD

AA, African American; W, white; BPAD, bipolar affective disorder; Behav, behavioural; Dis, disorder; Dep, depression; Disrup, disruptive; OCD, obsessive–compulsive disorder; Schiz, schizophrenia.

and two showed moderate adaptive intellectual disability.

Medications

Decisions to use medications for behavioural purposes were made in approximately quarterly (or more frequently as clinically indicated) multidisciplinary NBR conferences that occurred between the years 1994 and 2000. In these conferences, a careful weighing of the pros and cons of instituting, continuing, modifying or stopping psychotropic medications was made. Final authorization to use a medication for psychotropic purposes was obtained from subjects' guardians prior to beginning treatment. Ultimately, orders were written by the subjects' primary-care physicians, with dosing based on consideration of medical status, other medications utilized, and tolerance of the medication.

Those studied were most often placed on an SSRI or clomipramine because of an incomplete response to other psychopharmacological agents, or because of a desire to eliminate drugs that were causing or could cause unacceptable side-effects such as tardive dyskinesia. As shown in Table 2, of those studied, 14 received paroxetine, 9 received fluvoxamine, 7 received sertraline, 5 received fluoxetine, 1 received citalopram and 2 received clomipramine. Twenty-eight of those studied also received one or more other medications for psychotropic or anti-seizure purposes. These medications included thioridazine, mesoridazine, haloperidol, thiothixene, clonazepam, olanzapine, lithium, topiramate, depakote, propranolol, gabapentin and carbamazepine.

Prior to beginning the study, authorization to review subjects' records was obtained from the University of North Carolina at Chapel Hill Institutional Review Board and the Murdoch Center at Butner, North Carolina, Research Review Committee. All those studied had been administered a behavioural intervention programme (BIP) prior to beginning the study, and all continued on the BIP throughout the study.

NBR record evaluations

Utilizing retrospective reviews (see Janowsky et al., 2003), the NBR conference records of the 38 residents of Murdoch Center to whom a serotonergic antidepressant had been administered between years 1994 and 2000, and who were still continuing to receive psychotropic medications in the year 2000 were systemically reviewed. The NBR conferences consisted of required meetings of a subject's treatment team, which occurred approximately quarterly or more frequently depending on clinical considerations. In the NBR conference, the treatment team, consisting of a cottage manager, psychologist, nurse(s), nursing assistant(s), primary-care physician, pharmacist, educator and consulting psychiatrist reviewed the progress and evaluated responses to psychotropic medications of the individuals in question, focusing on overall behaviour and specific target behaviours.

The conference had a special focus on the utilization of medications given for the purpose of minimizing maladaptive behaviours. During each conference, a written summary reviewing the course and changes since the last NBR was presented by the nursing and other treatment staff. The summary consisted of: (1) the subject's behavioural diagnosis, (2) psychotropic and other medications given and changes in medications made since the last NBR conference, (3) significant adverse or side-effects noted since the last review, (4) significant laboratory tests and serum drug levels noted, (5) weight changes (data obtained monthly), (6) details of changes in target symptoms, (7) any changes in behavioural intervention plans, (8) monitoring methods and (9) progress towards goals and continuing status of skills. A verbal summary of progress was also given by the treatment staff, and a longitudinal quantitative graphing of specific target behaviours was provided by the unit psychologist.

From this NBR conference a permanent report was generated by the consulting psychiatrist or by the subjects' primary-care physician when the psychiatrist was not present, and it was these NBR conference reports that were reviewed as sources of data for the current study.

Psychologists' ratings

The frequency of aggressive, self-injurious and disruptive/destructive target behaviours was evaluated by totalling the cumulative longitudinal graphed observations of specific target behaviours, as provided at the NBR conferences by the unit psychologists. The cumulative number of recorded specific target behaviours, as graphed by the unit psychologist was evaluated for the month before beginning the serotonergic antidepressant (baseline) and the month leading up to the last reviewed NBR following the administration of a serotonergic antidepressant. In addition, a 'most severe behavioural score' was recorded, consisting of the baseline behaviour which had the highest frequency. Not all target behaviours occurred in every subject, and the methods of evaluation for a given

Table 2. Serotonergic antidepressants and concomitant psychotropic medications given to 38 developmentally disabled adults

Case no.	Medication	Post-drug time 1[a] (+3.39 mo.)	Post-drug time 2 (+6.24 mo.)	Other psychotropics	
				Baseline	Post-drug time 1 or 2
1	Paroxetine	20 mg	30 mg	Lithium, Depa	Same
2	Fluvoxamine	12.5 mg	12.5 mg	Top	Same
3	Fluvoxamine	12.5 mg	50 mg	Thior	Same
4	Paroxetine	20 mg	40 mg	Thior	Same
5	Fluvoxamine	125 mg	200 mg	Thior	Same
6	Paroxetine	20 mg	30 mg	Thior	Same
7	Paroxetine	10 mg	20 mg	Lithium	Lithium, Gaba
8	Paroxetine	20 mg	20 mg	Carb	Same
9	Fluvoxamine	12.5 mg	12.5 mg	None	None
10	Sertraline	100 mg	50 mg	Lithium, Carb	Same
11	Paroxetine	10 mg	20 mg	None	None
12	Sertraline	75 mg	75 mg	None	None
13	Fluoxetine	5 mg	5 mg	Clonazepam	Same
14	Clomipramine	75 mg	125 mg	Mesoridazine, Carb	Same
15	Fluvoxamine	25 mg	25 mg	Thiot	Same
16	Paroxetine	20 mg	20 mg	None	None
17	Fluvoxamine	12.5 mg	12.5 mg	None	Temazepam
18	Sertraline	50 mg	75 mg	Thiot, Lithium, Depa	Same
19	Fluoxetine	2 mg	8 mg	None	None
20	Fluvoxamine	25 mg	25 mg	Thiot, Lithium, Prop	Same
21	Paroxetine	20 mg	30 mg	Haloperidol, Carb[b]	Same
22	Paroxetine	20 mg	–	Haloperidol	–
23	Fluoxetine	20 mg	20 mg	Thior	Same
24	Fluvoxamine	25 mg	100 mg	Haloperidol, Thior	Same
25	Sertraline	125 mg	200 mg	Carb	Same
26	Paroxetine	20 mg	40 mg	None	Lorazepam
27	Clomipramine	50 mg	75 mg	Haloperidol, Depa[c]	Same
28	Fluoxetine	20 mg	20 mg	Depa	Same
29	Sertraline	50 mg	50 mg	Thior, Lithium	Same
30	Sertraline	50 mg	50 mg	Depa	Same
31	Paroxetine	20 mg	20 mg	Thior[c], Olan[b], Top	Same
32	Citalopram	20 mg	–	Prop	–
33	Paroxetine	20 mg	–	Thior, Gaba	–
34	Fluvoxamine	12.5 mg	12.5 mg	None	None
35	Paroxetine	20 mg	–	None	–
36	Fluoxetine	40 mg	40 mg	Thior, Carb	Thior
37	Sertraline	100 mg	100 mg	None	None
38	Paroxetine	20 mg	20 mg	Thior, Lithium	Same

Depa, depakote; Carb, carbamazepine; Gaba, gabapentin; Thior, thioridazine; Thiot, thiothixene; Prop, propranol; Olan, olanzapine; Top, topiramate.

[a] Mean time in months (mo.) after beginning antidepressant medications.

[b] A decrease in dosage occured.

[c] An increase in dosage occured.

target behaviour differed from unit to unit, psychologist to psychologist, and between the individuals observed. Longitudinal graphs were obtained for 14 of the 38 subjects (see Table 3).

Global ratings

NBR summaries were retrospectively evaluated for overall severity of maladaptive symptoms by one of us

Table 3. Psychologists' cumulative aggressive, self-injurious, destructive/disruptive and most severe scores in the month before baseline and in the month before the last Neuropsychiatric Behavioural Review (NBR) in 14 out of 38 intellectually disabled adults

Case no.	Most severe		Aggression		SIB		Destruction/ Disruption	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
2	40	5	0	0	40	5	–	–
9	60	35	1	0	60	35	–	–
10	200	48	0	0	–	–	200	48
13	500	50	20	25	500	50	–	–
17	70	50	–	–	6	6	70	50
25	25	2	8	5	25	2	5	0
26	10	0	–	–	–	–	10	0
28	15	30	15	30	–	–	12	5
29	29	9	2	0	–	–	29	9
31	30	20	5	2	–	–	30	20
33	21	4	–	–	–	–	21	4
34	31	4	–	–	31	4	–	–
35	17	15	–	–	15	20	17	15
36	10	2	10	2	–	–	2	1
Means	75.6	19.6	6.8	7.1	96.7	17.4	39.6	15.2

SIB, Self-injurious behaviour.
Scales utilized by the psychologists varied from person to person and from unit to unit. Pre = the cumulative ratings of the month before the baseline NBR; post = the cumulative ratings of the month before the last NBR during which antidepressants were administered (i.e. the last evaluated post-drug time-point).

(D.S.J.) using a 1- to 7-point global behavioural rating scale. For this scale, 1–2 = none to mild symptoms, 3–5 = moderate symptoms, and 6–7 = severe symptoms. Since in initially constructing the global scale we were not sure that we could accurately discriminate at the lower end of the scale, a plus (+) or minus (−) was utilized. For purposes of data analysis, each (+) added 0.25 points, and each (−) subtracted 0.25 points. The global severity scale roughly paralleled the Severity of Illness component of the Clinical Global Impressions Scale (NIMH, 1985).

Quotes from NBR records illustrating mild and severe symptoms respectively are as follows:

Case no. 4 (*Baseline*)

has had minor aggressions. However, has been doing well in terms of aggression and more worrisome behaviours (score = 2.0).

Case no. 25 (*Baseline*)

continues to have marked tissue injury which has resulted in medical treatment. Continues to have significant aggression toward others (score = 6.25).

For purposes of data analysis of the 1- to 7-point global behavioural rating scale, NBRs were divided into four time-points. The 'Pre-baseline' time-point was the NBR closest to 3 months before beginning the serotonergic antidepressant [mean = -3.04 ± 0.82 months (mean ± S.D.)]. The 'Baseline' time-point was the NBR occurring just prior to starting serotonergic antidepressants. 'Post-drug time 1' was the NBR closest to 3 months after beginning antidepressant treatment (mean = $+3.39 \pm 0.83$ months) and 'Post-drug time 2' was the NBR closest to 6 months after beginning serotonergic antidepressants (mean = $+6.24 \pm 1.55$ months). Not all subjects had data for the Pre-baseline time-point or Post-drug time 2, but all had data for the Baseline and Post-drug time 1 time-points (see Table 4).

In addition to the global behavioural ratings, aggression, SIB, destruction/disruption and depression/dysphoria were evaluated by one of us (D.S.J.) using the 1- to 7-point scale if these behaviours were mentioned in a given NBR report (see Table 5).

To ascertain the reliability of the behavioural ratings made by the first author (D.S.J.), two of the authors [rater no. 1 (M.S.) and rater no. 2 (J.M.D.)] independently rated approx. 20% of the quarterly NBR evaluations. For the global behavioural rating scale, Pre-baseline, Baseline, Post-drug time 1, and Post-drug time 2 ratings for rater no. 1 correlated 0.86, 0.93, 0.82, 0.96 respectively with those of the first author. For rater no. 2 these correlations were 0.98, 0.92, 0.97 and 0.89. In addition, rater no. 2 evaluated the above subgroup of NBRs for aggression, SIB, destruction/disruption and depression/dysphoria. These ratings were correlated with the first author's ratings. Inter-class correlations were calculated by a two-way mixed-effects model with subjects randomized and measures fixed. The inter-class correlations for aggression, SIB, destruction/disruption and depression/dysphoria were 0.96, 0.83, 0.75 and 0.75 respectively.

Statistical analysis

Changes in the psychologists' ratings were evaluated using the Wilcoxon matched-pairs sign-rank test. With respect to the global ratings, since the variance of the different time phases was equal (Wilcoxon test), as determined using Levine's test of homogeneity of variance ($p = 0.162$) we proceeded with an analysis of

Table 4. Global ratings of 38 intellectually disabled adults before and after receiving serotonergic antidepressants

Case no.	Pre-baseline (−3.04 mo.)	Baseline	Post-drug time 1 (+3.39 mo.)	Post-drug time 2 (+6.24 mo.)	% Change (Baseline to Post-drug time 1)	% Change (Baseline to Post-drug time 2)
1	1.75	2.00	1.00	2.75	−50	+38
2	–	3.25	2.25	2.25	−31	−31
3	3.00	3.00	3.00	2.00	0	−33
4	1.75	2.00	2.00	1.25	0	−38
5	3.25	2.75	2.25	2.25	−18	−18
6	2.25	2.25	2.25	1.25	0	−44
7	3.25	3.25	2.25	2.25	−31	−31
8	3.25	3.75	2.75	2.25	−27	−40
9	4.25	6.00	5.00	5.00	−17	−17
10	4.00	3.25	3.00	2.75	−8	−15
11	–	4.25	2.25	2.25	−47	−47
12	–	4.25	2.25	2.75	−47	−35
13	6.00	6.00	2.25	3.00	−63	−50
14	3.25	4.00	4.00	4.00	0	0
15	6.00	6.00	2.25	3.00	−63	−50
16	3.00	3.00	1.75	1.75	−42	−42
17	3.25	3.25	2.75	2.00	−15	−38
18	3.75	3.75	3.00	2.00	−20	−47
19	–	3.25	3.25	3.00	0	−8
20	4.75	6.25	2.25	3.25	−64	−48
21	4.00	4.25	3.00	2.75	−29	−35
22	3.00	3.75	3.75	–	0	–
23	3.75	3.75	3.00	4.25	−20	+13
24	5.00	6.00	4.00	4.25	−33	−29
25	6.00	6.25	4.25	3.25	−32	−48
26	–	3.25	1.75	1.25	−46	−62
27	2.75	3.75	3.75	3.25	0	−13
28	–	3.25	2.00	3.25	−38	0
29	2.25	3.75	2.25	2.75	−40	−27
30	4.00	3.75	3.25	2.25	−13	−40
31	4.00	4.25	3.25	3.25	−24	−24
32	3.00	5.00	2.25	–	−55	–
33	5.00	4.00	4.25	–	+6	–
34	6.00	6.00	2.25	2.25	−63	−63
35	–	4.75	5.75	–	+21	–
36	5.25	6.00	5.00	2.75	−17	−54
37	3.75	4.00	3.25	3.00	−19	−25
38	–	4.25	4.25	3.00	0	−29
Means	3.8	4.1	2.9	2.7	−24.8%	−30.3%

Global severity was rated on a 1- to 7-point scale ranging from none to severe maladaptive behaviour. Percentages rounded off to nearest whole number.

variance to see if any difference existed between the various means. A post-hoc analysis of the difference between the time-points was determined using a Bonferroni (Dunn) *t* test, since the numbers in each group compared differed.

Percentage changes between Baseline and the global behavioural ratings for Post-drug time 1 and Post-drug time 2 respectively were calculated for each subject, and differences between the number of subjects showing a $\geqslant 25\%$ decline in scores vs. the number

Table 5. Ratings for specific behaviours before and after receiving serotonergic antidepressants in 38 developmentally disabled adults

Case no.	Most severe		Aggression		SIB		Disruption		Depression	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	2.25	1.75	–	–	–	–	–	–	2.25	1.75
2	3.00	2.00	3.00	2.00	3.00	2.00	–	–	–	–
3	4.00	2.75	1.25	1.25	–	–	4.00	2.75	–	–
4	2.25	2.00	2.25	2.00	–	–	–	–	–	–
5	3.25	3.25	–	–	–	–	3.25	3.25	–	–
6	3.00	1.75	–	–	–	–	2.25	3.25	3.00	1.75
7	3.25	1.75	–	–	–	–	–	–	3.25	1.75
8	3.25	2.25	2.75	3.25	3.25	2.25	–	–	3.00	1.75
9	6.25	4.25	–	–	6.25	4.25	–	–	2.75	2.25
10	4.00	3.00	–	–	–	–	4.00	3.00	–	–
11	4.25	2.25	–	–	–	–	4.25	2.25	–	–
12	5.00	3.00	–	–	–	–	–	–	5.00	3.00
13	6.00	3.00	5.00	3.00	6.00	3.00	–	–	–	–
14	4.00	4.00	–	–	3.00	3.00	4.00	4.00	–	–
15	6.00	2.75	6.00	2.75	–	–	–	–	–	–
16	3.00	1.25	–	–	–	–	3.00	1.25	3.00	1.25
17	3.00	2.00	–	–	–	–	3.00	2.00	–	–
18	3.25	2.00	2.25	1.00	3.25	2.00	–	–	3.25	2.00
19	3.75	3.00	–	–	1.00	1.00	3.75	3.00	3.75	3.00
20	5.00	3.00	5.00	3.00	5.00	3.00	5.00	3.00	–	–
21	5.00	4.00	–	–	5.00	4.00	–	–	3.25	2.00
22	2.75	2.75	–	–	2.75	2.75	–	–	–	–
23	4.00	4.25	–	–	–	–	–	–	4.00	4.25
24	6.00	4.00	–	–	6.00	4.00	–	–	–	–
25	7.00	3.25	7.00	3.25	6.00	3.00	5.00	2.25	–	–
26	3.25	1.75	–	–	–	–	–	–	3.25	1.75
27	2.25	3.00	2.75	3.00	–	–	2.75	2.75	–	–
28	3.00	3.00	–	–	–	–	3.00	3.00	3.00	2.00
29	3.25	2.25	–	–	–	–	3.25	2.25	–	–
30	3.00	2.25	–	–	–	–	3.00	2.25	–	–
31	4.25	3.00	2.75	2.25	–	–	–	–	4.25	3.00
32	4.00	2.00	–	–	3.00	2.00	4.00	2.00	4.00	2.00
33	3.25	5.25	1.25	3.00	1.75	3.25	3.25	5.25	–	–
34	6.75	2.00	5.00	2.00	6.75	2.00	5.00	2.00	–	–
35	4.00	5.00	–	–	–	–	4.00	5.00	–	–
36	5.75	2.25	5.75	2.25	–	–	–	–	5.00	1.75
37	3.25	2.25	3.25	2.25	3.25	2.25	3.25	2.25	–	–
38	5.25	3.00	2.75	2.25	4.00	2.75	3.00	2.25	5.25	3.00
Means	4.04	2.79	3.62	2.41	4.07	2.73	3.62	2.80	3.60	2.25

SIB, Self-injurious behaviour.
Each specific behaviour was rated on a 1 - to 7-point scale; Pre = baseline, Post = last evaluated post-drug time-point (i.e. post-drug time 1 or 2).

showing a $\geqslant 25\%$ increase in scores were compared using a sign test.

In addition, baseline post-differences between various specific behaviours (i.e. aggression, SIB, destruction/disruption, depression/dysphoria and 'most severe' behavioural score') were evaluated using the Wilcoxon matched-pairs sign-rank test, comparing Baseline with the last evaluated post-drug

NBR (i.e. either Post-drug time 1 or Post-drug time 2). Significance was set at an alpha of 0.05 or lower using two-tailed tests.

Results

Table 3 presents the psychologists' longitudinal behavioural ratings of the target symptoms of aggression, SIB, destruction/disruption and the most severe behavioural score. Cumulative ratings for the month before beginning serotonergic antidepressants and the month before the last evaluated NBR after the beginning of serotonergic antidepressants were compared. An overall decrease in the 'most severe behavioural score' was statistically significant ($p<0.001$, Wilcoxon sign rank test). The changes in scores of the psychologists' aggression ratings was not significant ($p=$ns). SIB ratings decreased significantly ($p=0.048$), as did destruction/disruption ratings ($p=0.005$).

Table 4 outlines the individual global behavioural rating scale scores and their group means $\pm$ standard deviations obtained from the NBRs occurring before and after beginning serotonergic antidepressants. Overall, a significant change over time occurred in the global behavioural ratings as determined by one-way ANOVAs ($F_{1,3}=12.81$, d.f.$=3$, $p<0.0001$). Since the one-way ANOVA revealed a significant overall difference in the means at the different time-points, we determined which individual means for a given time-point differed from the others. We ran multiple comparisons of the means using the Bonferroni (Dunn) t test, since the numbers in each group differed from each other. The differences in means between the Pre-baseline and Baseline time-points and Post-drug time 1 and Post-drug time 2 respectively were not statistically significant. The difference between the Pre-baseline ratings and Post-drug time 1 was statistically significant ($p=0.014$), as was the difference between the Pre-baseline time-point and Post-drug time 2 ($p<0.001$). The difference between the Baseline time-point and Post-drug time 1 was statistically significant ($p<0.001$), as was the difference between the Baseline time-point and Post-drug time 2 ($p<0.001$).

As shown in Table 4, by defining antidepressant efficacy as a decrease of 25% or more in the global behavioural score between the Baseline time-point and Post-drug time 1, 18 out of 38 (47.4%) showed a $\geqslant$25% decrease in global behavioural ratings (mean decrease $=-24.8$%) and six of this group showed decreases of 50% or more. Comparing the Baseline ratings with Post-Drug time 2, 24 out of 34 subjects (70.6%) showed a decrease of 25% or more (mean decrease $=-30.3$%), and five showed a decrease of 50% or more. In contrast, only one individual showed a clinically significant increase in the global rating scale of $>$25% (significance on exact binomial distribution, $p<0.0001$ and $p<0.0001$ respectively).

Table 5 shows the ratings of the Baseline time-point and Post-drug time 1 or Post-drug time 2, whichever occurred last, for aggression, SIB, destruction/disruption and depression/dysphoria and the 'most severe' behavioural score, as rated by D.S.J. Significant decreases occurred in aggression ($p=0.007$), SIB ($p<0.001$), destruction/disruption ($p<0.015$), depression/dysphoria ($p<0.001$), and 'most severe behavioural' ($p<0.001$).

Several physical and behavioural side-effects were observed during administration of the serotonergic antidepressants. Acne occurred in one individual and constipation occurred in another. Administration of serotonergic antidepressants led to a significant worsening of target symptoms in four of the subjects (subject nos. 22, 23, 33, 35), eventually leading to a termination of medications. In addition, subject no. 3 had previously experienced a similar negative reaction to fluoxetine, but later tolerated fluvoxamine, and subject no. 32 showed an increase in symptoms with fluoxetine, but later tolerated citalopram. Twenty-four individuals had NBR reports that contained enough data to compare baseline weights with weights after serotonergic antidepressant administration. Baseline weights averaged 131.5 lb, whereas post-antidepressant (Post-drug times 1 or 2) weights averaged 135.4 lb. Seven of the subjects gained 10 lb or more after beginning antidepressant therapy, whereas only one lost 10 lb or more. No increase in seizure activity was noted during serotonergic antidepressant administration, nor was there a need to increase anti-seizure medications.

Discussion

This paper outlines our evaluation of the administration of serotonergic antidepressants in an institutionalized intellectually disabled population. The decision to begin a SSRI or clomipramine was based on clinical factors. In our evaluation, we did not exclude any subjects based on diagnosis, age, level of intellectual disability, or associated neurological symptoms. Thus, this study reflects the 'real world' of treatment of institutionalized people who are severely or profoundly intellectually disabled and who have maladaptive behaviours.

The principal finding of this study is that serotonergic antidepressants caused a statistically significant

decrease in the psychologists' behavioural ratings, in global ratings of maladaptive behaviour and in aggressive, self-injurious, and destructive/disruptive behaviours and in depression/dysphoria. Analysis of individual results showed that a significant percentage of the study population had a clinically significant (>25%) reduction in their global ratings. Responders did not appear to differ from non-responders on any of the demographic or diagnostic characteristics examined, or on the drug or the drug doses used.

The antidepressants in the doses used were relatively well tolerated, with the majority of those treated remaining on medication for 6 months or more. Overall, improvement continued over the 6-month study period, with little evidence of tolerance development. However, several of the subjects experienced an activation of target symptoms while on serotonergic antidepressant medications, leading to medication discontinuation.

The current study has a number of limitations. The group studied was relatively small, in spite of the study having been the largest we have found performed to date. The results were based on data obtained retrospectively from chart reviews. Behavioural data were not formally correlated with information related to the status of each patient's affective disorder or other symptoms (i.e. sleep patterns, affective state, etc.). Many of the subjects required and were administered additional psychotropic medications and/or anti-seizure medications before or while being given antidepressant drugs. It is likely that partial therapeutic effects had been reached by the administration of these psychotropic medications in many of the subjects before antidepressant medication was started.

In a minority of our subjects other psychotropic drugs were changed or started during the time that the serotonergic antidepressants were administered (see Table 2). Therefore, in such cases, attribution of ameliorative effects to a serotonergic antidepressant was complicated by the possible therapeutic effects of the additional medication or medication changes. Furthermore, in cases where other psychotropic medications were administered prior to the time that a serotonergic antidepressant was given, addition of a serotonergic antidepressant could have led to metabolic changes leading to increased and/or more effective blood levels of the original compound or vice versa, or to synergistic effects.

Surprisingly few side-effects were noted in the study following serotonergic antidepressant administration. The fact that those studied were largely non-verbal may have, in part, led to an under-reporting of drug side-effects. Also, the nursing staff tended to note only serious side-effects at the NBR conferences. Since no formal monitoring system focusing on side-effects was in place, it is difficult to tell if more subtle side-effects actually occurred and were not detected.

The study did not include placebo controls, and no blinding of drug treatment occurred. However, conversely, the treated individuals were not subjected to the disadvantages of a washout period, such as occurs in most controlled studies. A washout strategy has the potential for causing an increase in baseline symptoms due to withdrawal (i.e. rebound) effects or the unmasking of suppressed symptoms. An on/off/on design, with antidepressant added to existing treatments would have added valuable data as to improvement or worsening. Alternatively, an add-on design, giving either serotonergic antidepressant or placebo on a blinded basis and keeping all other medications unchanged might also have yielded useful data.

Although multiple drugs were often used in the treatment of our subject group, thus making difficult the ascertainment of 'pure' effects, this situation does approximate the clinical situation that occurs commonly when challenging behaviours exist. In addition, since the subjects were all being treated with BIPs, our study actually is a trial of antidepressant medications given jointly with behavioural interventions and is not a 'pure' medication trial as such.

In our study, the nature of specific target behaviours varied from person to person. Use of standardized rating scales would have added an important analytical dimension, augmenting the more idiosyncratic but well-tailored observations that were made.

It should be noted that our subject group scored on average in the middle range of the 1- to 7-point global behavioural rating scale. Thus, for the most part, the subjects showed a moderate degree of maladaptive behaviours at baseline and the decrease in the behaviours following antidepressant treatment was relatively small. Conversely, however, even small changes in challenging behaviours may be clinically significant.

Since most of the subjects were non-verbal, as well as severely or profoundly retarded, clinical diagnoses had been made relying heavily on observations of changes in rates of target behaviours, cyclic withdrawal or crying, whining, agitation or cyclic associated sleep disturbances. These diagnoses were obviously more impressionistic and less reliable than would occur in general psychiatric or more verbal populations.

It is important to note that developmentally disabled populations may have distinct sensitivities and

adverse reactions to psychotropic medications, due to central nervous system damage, metabolic, pharmacodynamic and pharmacokinetic differences. This population, being as vulnerable as it is and lacking legal competence, requires special consideration before any psychotropic medication is started, and requires subsequent careful review and monitoring once administration begins.

In spite of the above limitations, our observations do suggest that overall, serotonergic antidepressants, at the doses given in our study, improve maladaptive behaviours in a population of developmentally disabled adults. This improvement continued over a period of at least 6 months. Further prospective studies are suggested, using a larger number of individuals, placebo controls, and possibly a more disturbed subject population.

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Statement of Interest

Dr Janowsky serves as a consultant to Glaxo-SmithKline.

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