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Polypharmacy-induced cognitive dysfunction and discontinuation of psychotropic medication: a neuropsychological case report

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***Abstract*:** Polypharmacy is common in patients with a diagnosis of bipolar disorder. Although polypharmacy is known to increase the risk of iatrogenic neurological conditions, the recovery of cognitive function after drug withdrawal has been rarely documented in psychiatric patients using standardized neuropsychological methods. We present a neuropsychological case report of patient SN, a 41-year-old woman who developed a socially and occupationally detrimental condition of cognitive dysfunction likely induced by long-term exposure to lithium and other psychiatric medications. To shed light on SN's cognitive deficits and their recovery after drug withdrawal, neuropsychological assessments were conducted before, and approximately 2 years after, lithium and other psychiatric drugs were discontinued. Selective cognitive impairments were observed before drug discontinuation in visuomotor speed, visuoperceptual reasoning and delayed visual memory. Partial, but not complete, recovery of function was observed 2 years after drug withdrawal.

Keywords: bipolar disorder, brain disorders, case report, cognitive impairment, lithium, polypharmacy

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Introduction

Psychiatric patients often receive psychotropic drugs in combinations that are not always supported by evidence.[1,2] Although this situation is not new,[3] the median number of medications prescribed in psychiatric outpatient visits has increased further and substantially from the late 1990s.[4] While the use of more than one medication may sometimes be warranted, polypharmacy is generally associated with a higher risk of serious adverse effects and iatrogenic harm,[5–7] including neurological injury.[8]

Today, nearly all bipolar disorder patients are prescribed drugs from more than one class within a year from their first diagnosis.[9] Many of the pharmacological agents commonly prescribed for this diagnostic group, such as lithium and antipsychotics, carry the risk of cognitive side-effects.[10–14] Long-term lithium treatment has been associated with cases of iatrogenic neurological conditions of varying degree.[15–19] Similarly, high doses of antipsychotics have been linked to impaired cognitive function,[20,21] and cumulative exposure to antipsychotics has been associated with decreased cognitive performance over time.[22] Polypharmacy heightens potential risks for brain and cognition; both antipsychotics and antidepressants, for example, can increase the toxicity of lithium when used in combination.[8,23,24]

When iatrogenic neurological problems occur, neuropsychological assessments are important for identifying cognitive deficits, discerning their etiology and monitoring recovery after drug withdrawal. Published case reports concerning such conditions, however, commonly focus on obvious neurological and somatic symptoms and rarely use standardized neuropsychological methods.[15,25–27] Detailed neuropsychological data are therefore

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mostly lacking, making cases of iatrogenic conditions challenging for clinicians to identify. Evidence suggests that lithium-induced and polypharmacy-related iatrogenic neurological conditions are challenging to identify at their early stages,[15,28] and they are frequently misdiagnosed as aphasia,[29,30] Alzheimer's disease,[31] frontotemporal dementia,[32] Parkinson's disease,[33] or other forms of progressive brain disorder.[7,34–37]

Detailed neuropsychological assessments describing the recovery of cognitive function after drug discontinuation are similarly rare. While severe lithium intoxication has been associated with persistent cognitive defects in cases of profound neurological damage,[38–41] discontinuation studies suggest that less severe cognitive deficits can improve when lithium is withdrawn.[42,43] Similarly, the use of antipsychotics can lead to irreversible neurological conditions,[44] but the discontinuation of antipsychotics has been associated with improved cognitive performance in a recent naturalistic study,[45] although the study design precluded inferences about causal direction.

In this study, we describe a neuropsychological case of cognitive dysfunction and partial recovery of function in a premorbidly cognitively high-achieving 41-year-old woman prescribed a combination of psychiatric drugs over the long term. Our patient, SN, suffered from cognitive deficits that emerged gradually several months after the initiation of lithium and several years of long-term treatment with other psychiatric drugs. Although the condition was far less extreme than those described in cases of severe lithium intoxication,[38,39] the cognitive impairments disabled her from functioning in her normal occupational and social roles. After lithium and other psychiatric medications were withdrawn, however, she was able to return to work and resume her normal social responsibilities, strongly suggesting that the condition was drug-related.

To shed light on the detailed pattern of cognitive impairment and recovery, we report results from two neuropsychological assessments, conducted immediately before and approximately 2 years after psychiatric polypharmacy was discontinued. Concurrently with lithium, SN had been prescribed citalopram and a low dose of quetiapine, both of which she had taken for years, and zopiclone that she had been prescribed for sleep. She had also been prescribed alprazalone, which she took rarely, and levothyroxine to treat hypothyroidism, a side-effect of lithium.

Materials and methods

Case report

SN is a right-handed woman with a doctoral degree, 41 years old at the time of the first neuropsychological evaluation. She was referred for neuropsychological assessment at the Helsinki City Health Center in January 2015 because of self-reported cognitive problems related to memory, visual attention, and speech production that interfered with her ability to carry out her responsibilities at work. She had no history of neurological illness or substance abuse. She had been a high-achieving student throughout her primary and secondary education; she had graduated from high school with an exceptionally high GPA (9.6/10.0) and with the highest possible grades in all six of the tested subjects in the Finnish high school matriculation exam. She had been successfully employed throughout her adult life in several positions in a cognitively demanding occupation. In addition, she completed her PhD while working full time. According to her own report, she had never taken a single day of sick leave from work in her life before.

SN had originally been diagnosed with 'depressive neurosis' (*neurosis depressiva*) as a university undergraduate student in 1994. She saw a psychotherapist for 2 years and was also prescribed a benzodiazepine (alprazolam) and later a tricyclic antidepressant (clomipramine hydrochloride), for concerns related to family and childhood issues and uncertainty about her studies. She was able to continue her studies, and the medications were discontinued. She later underwent two additional periods of psychotherapy, and was started on a selective serotonin reuptake inhibitor (SSRI) antidepressant in 2005 (citalopram 20 mg, later 50 mg once a day). Her psychiatric complaints had never been severe, however, and never disabled her from working or taking care of her children. Her diagnosis was changed to bipolar disorder in 2008, somewhat surprisingly, considering that she did not have complaints about elevated mood, had never experienced overtly manic symptoms, been hospitalized or had her relationships or work affected by manic symptoms, and a low dose of quetiapine was initiated (25 mg once or twice a day) (1). The bipolar diagnosis was

made provisionally at the time, and it was likely incorrect. It was removed in 2015 at SN's request.

Lithium was started in August 2013 (lithium carbonate 300 mg 3–4 times a day) because of SN's complaints of weight gain from quetiapine. The treating psychiatrist's plan was to substitute lithium for quetiapine, but in practice she was maintained on both (for reasons that are unclear). Before lithium was initiated, SN had never experienced any changes in her cognitive abilities that would have interfered with her ability to work. Gradually during the spring of 2014, about 4–8 months after lithium had been initiated, however, both SN and her partner became concerned of a decline in SN's everyday cognitive performance characterized by forgetfulness, problems in concentrating, visual attention, and using numbers. SN had been on leave from work to pursue a research project, but became unable to work due to her experienced cognitive problems. The problems continued when she returned to her regular occupation, where, in sharp contrast to her consistently reliable prior performance, she started missing agreed appointments and failed to carry out many of her responsibilities. SN's partner had to take responsibility of her financial affairs, because she was no longer able to use the online banking system, despite having used it for years. Both SN and her partner were concerned that her problems were signs of dementia or other neurological disease, as SN had not experienced any mood-related or psychiatric problems in a long time, and SN's partner alerted her to seek medical help.

After her first complaints of fatigue, sluggishness, and memory problems, laboratory tests in October 2014 revealed a thyroid-stimulating hormone (TSH) level of 9.83. She was diagnosed with hypothyroidism, a common side effect of lithium, and started on levothyroxine (0.05–0.1 mg once a day). By December, her test results had returned to the normal range (TSH 0.039; T4-V 14; TPOAb > 33). However, her cognitive problems persisted. She had to take sick leave from work, and she was referred for a neuropsychological evaluation.

The first neuropsychological assessment was conducted in January 2015, after lithium had been administered for 17 months and SN was still maintained on all psychiatric drugs. Her hypothyroidism, however, had already been treated successfully and her laboratory results had returned to normal levels. SN presented neither with any mood-related symptoms nor overt signs of neurological disease. She subjectively reported problems in speech production, using numbers, and remembering everyday appointments, to the extent that her partner had had to take increasing responsibility for their children's daily routines. SN reported that even cognitively trivial tasks such as using a weekly planner had become challenging.

A neurological examination in April 2015 found no indication of progressive neurological disease or signs of gross cognitive impairment (MMSE 30/30). According to the radiologist's report, an MRI examination showed normal findings with no signs of cerebellar, hippocampal or other changes, or of tissue loss. Laboratory tests of liver and thyroid function were in the normal range (ALT 69; GGT 36; T4-V 14; TSH 0.014). SN received a diagnosis of *F06.7, mild cognitive disorder / a dysfunction of memory and cognitive processing.*

As no other etiological factors were readily available, and no accidents, injuries, or other abrupt changes had occurred that could have provided an explanation for the cognitive problems, it seemed likely that SN's cognitive problems could be related to one or more of the psychiatric drugs she had been prescribed. Lithium was considered a likely suspect, as the cognitive problems had appeared gradually within about 6 months after lithium treatment was begun. A psychogenetic etiology seemed unlikely, as the latest instance of difficulties in SN's life had occurred 6 years prior to the current evaluation, but the cognitive problems, in contrast, had appeared only recently and fairly abruptly. Not only were any indications of abnormal fluctuations in mood lacking, but her bipolar diagnosis was also likely incorrect and removed altogether retrospectively.

During the first neuropsychological evaluation, SN was taking, concurrently with lithium, an antidepressant (citalopram 20 mg once a day) and a low dose of quetiapine (25–50 mg once a day; well below the recommended level for bipolar disorder).[46] In addition, she had been prescribed zopiclone and alprazolam for problems with sleep and to be taken only when needed (7.5 mg and 0.5 mg once a day, respectively; the latter she rarely took).

Lithium was tapered off over a period of 4 weeks after the first neuropsychological assessment in February 2015. After lithium had been withdrawn, all SN's other psychiatric medications were also

tapered off during February and March 2015 at her own request because she felt that she had had no psychiatric complaints in years apart from everyday life challenges. The tapering of the drugs was conducted under the supervision of a psychiatric outpatient clinic, where the process was begun by one psychiatrist and continued later by others (depending on who was available). In the beginning of the process, SN was given telephone appointments with a psychiatrist within 6–8 days after each dose reduction to monitor their effects.

When the tapering of lithium began, the dose (which had already been reduced once after the first testing) was reduced from 2.5 300-mg tablets once a day to two tablets a day. Six days later, the dose was reduced to one 300-mg tablet a day; 8 days after this to 150 mg once a day; and finally discontinued 14 days after this. The tapering of citalopram and zopiclone was begun when SN was still taking 150 mg of lithium. The citalopram dosage was halved every week (from 20 mg to 10 mg to 5 mg) and then discontinued. The zopiclone dose was first halved from 7.5 to 3.75 mg and then, 7 days after this reduction, further reduced from daily administration to once every 2 days and then discontinued 7 days later. Quetiapine was discontinued last. Three weeks after lithium, citalopram, and zopiclone had been withdrawn, SN called the outpatient clinic reporting problems of insomnia and waking up at night with restless, painful feelings in her legs and having to get up and walk around, occasionally for hours. She was prescribed melatonin to help with sleep.

After lithium, citalopram, and zopiclone had been withdrawn, SN initially reported feeling more energetic but felt that the memory and other cognitive impairments still persisted. It was only after several weeks or months that she felt that her memory problems considerably improved. She described the improvement as if a 'curtain of blur' had been removed cognitively. Levothyroxine was gradually decreased, and, in March 2015, SN was euthyroid (TSH = 0.014; T4-V = 14), and levothyroxine was discontinued.

The second neuropsychological assessment was conducted in 2017, 23–29 months after psychiatric drugs were withdrawn. While no evidence-based criteria are available, to our knowledge, for defining an unambiguously optimal time point for follow-up testing under these circumstances, it was considered important that the interval after drug withdrawal be sufficiently long both to allow adequate time for potential recovery of cognitive function and also to rule out the possibility that any improvements could be explained by practice effects alone. By the time of the second assessment, SN had fully resumed her normal roles in both her professional and personal life, and reported no problems in mood outside of the everyday range (despite having divorced her partner during this time). Subjectively she felt that her cognition had improved significantly. For practical reasons related to SN's availability, the assessment was conducted in three sessions in February (WAIS-IV), March (Trail Making, Symbol Search and Coding from WAIS-IV) and August (WMS-III; tapping; Matrices (2) from WAIS-IV).

Both assessments were conducted in SN's native language, Finnish, by the first author. SN gave informed consent to participate in the study and to allow her medical data to be published in anonymized form. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa and the Helsinki University Hospital.

Neuropsychological assessment

General intellectual abilities and memory function were assessed using the Finnish versions of the Wechsler Adult Intelligence Scale[47] (WAIS-IV; for administered subtests see Table 1) and the Wechsler Memory Scale[48] (WMS-III). Attention and executive function were assessed using the Trail Making Test[49] (TMT); the Mental Control subtest from the WSM-III; and the phonemic and categorical verbal fluency tasks. Motor function was assessed with the Finger Tapping Test.[50] At first evaluation, visuoconstructive function and visual memory were assessed using the Rey-Osterrieth Complex Figure Test,[51,52] and with direct copies of line drawings of three-dimensional shapes of a cube, a pyramid, and a Greek cross. Visuoconstructive abilities and judgment of line orientation were assessed using clock faces with and without hands, and asking SN to identify presented times of the day and to draw the hands indicating specified times.

On tests for which Finnish norms are not available, international norms were used (3). Test results (Rey Complex Figure; Similarities, Vocabulary, Information; Logical Memory I and II; Visual Reproduction I and II) were scored independently by the two authors, one of whom

Table 1. SN's neuropsychological test results immediately before and 23–29 months after psychiatric medications were discontinued.

	First assessment *(drugs maintained)*		**Second assessment *(23–29 months after withdrawal)***	
	Score	**Percentile**	**Score**	**Percentile**
WAIS-IV indexes				
Verbal comprehension	132	98	137	99
Perceptual reasoning	104	61	116	87
Working memory	120	92	126	96
Processing speed	92	33	106	68
Full scale[a]	117	88	129	97
WAIS-IV subtests				
Similarities	12	25–75	13	75–91
Vocabulary	19	⩾98	17	⩾98
Information	15	91–98	16	91–98
Block design	11	25–75	12	25–75
Visual puzzles	10	25–75	13	75–91
Arithmetic	12	25–75	12	25–75
Digit span	15	91–98	17	⩾98
Coding	7	9–25	12	25–75
Symbol search	10	25–75	10	25–75
WMS-III indexes				
Auditory immediate	139	99.5	142	99.7
Visual immediate	115	89	124	97
Immediate memory	131	99	138	99.5
Auditory delayed	127	99	127	99
Visual delayed	112	82	137	99.5
General memory	130	99	141	99.9
WMS-III subtests				
Logical memory I	16	91–98	17	⩾98
Logical memory II	15	91–98	15	91–98
Verbal paired associates I	17	⩾98 (ceiling)	17 (ceiling)	⩾98
Verbal paired associates II	14	⩾75 (ceiling)	14 (ceiling)	⩾75
Word list I	15	91–98	16	91–98
Word list II	15	91–98	17	⩾98

(Continued)

Table 1. (Continued)

	First assessment *(drugs maintained)*		Second assessment *(23–29 months after withdrawal)*	
	Score	**Percentile**	**Score**	**Percentile**
Faces I	14	75–91	17	⩾98
Faces II	14	75–91	18	⩾98
Family pictures I	11	25–75	11	25–75
Family pictures II	10	25–75	11	25–75
Visual reproduction I	17	⩾98	13	75–91
Visual reproduction II	7	9–25	11	25–75
Mental control	12	25–75	15	91–98
TMT				
TM A	30	70	19	>99
TM B	62	90	43	>99
TM B-A	32	90	24	>99
TM B/A	207	80	226	70
Finger tapping (10 s, mean 3 trials)				
Right hand	46	normal range	48	normal range
Left hand	37	normal range	43	normal range
Verbal fluency (60 s)				
Phonemic ('k')	21	>90	n/a[c]	n/a
Phonemic ('s')	21	>90	n/a	n/a
Semantic (animals)	31	>90	n/a	n/a
Line drawings, direct copy	3/3	not impaired	n/a	n/a
Rey-Osterrieth Complex Figure				
Direct copy	35/36	90	n/a	n/a
From memory, immediate	20/36	5–10	n/a	n/a
From memory, delayed (85 min) [b]	17.5/36	5–10	n/a	n/a
Clock hands and faces				
Clock hands	8/8	not impaired	n/a	n/a
Clock faces	8/8	not impaired	n/a	n/a

[a]Full-scale IQ estimated as instructed in the manual, by calculating the means for each index and substituting the subtest average for subtests that were not administered.
[b]The published norms for delayed recall are for a 30-min delay.
[c]Not administered.
IQ, intelligence quotient; TMT, Trail Making Test; WAIS-IV, Wechsler Adult Intelligence Scale; WMS-III, Wechsler Memory Scale.

Table 2. Index and subtest level discrepancy comparisons on the WAIS-IV.

		First assessment			Second assessment		
	Critical value 0.05	Difference	Base rate full sample	Base rate reference group	Difference	Base rate full sample	Base rate reference group
VCI-PRI	16.89	28[a]	2.6	0.0	16	15.5	8.7
VCI-WMI	16.64	12	24.0	21.7	6	35.8	30.4
VCI-PSI	16.89	40[a]	1.5	0.0	26[a]	9.0	10.1
PRI-WMI	14.71	−16[a]	15.9	14.5	−10	28.1	24.6
PRI-PSI	15.00	12	24.4	31.9	10	28.4	37.7
WMI-PSI	14.71	28[a]	6.0	8.7	20[a]	11.5	17.4
Digit span - arithmetic	2.61	3[a]	19.8		5[a]	6.1	
Symbol search - coding	2.54	3[a]	15.3		−2	27.3	

[a]Indicates a statistically significant difference at the 0.05 level. Base rates indicate cumulative percentages in the full Finnish standardization sample and in the reference group (FSIQ > 120).
FSIQ, full-scale intelligence quotient; PRI perceptual reasoning index; PSI, processing speed index; WAIS-IV, Wechsler Adult Intelligence Scale; WMI, working memory index; VCI, verbal comprehension index.

was blind to time of assessment. The blinding was conducted separately for each subtest to prevent the blind from breaking unintentionally. Because the original testing session had not been recorded, the second rater scored SN's responses on verbal tasks on the basis of the first rater's notes. While particular care had been taken to make detailed notes of SN's verbatim responses, the second rater's scorings of SN's performance on verbal tasks were thus not entirely independent of the first rater. Mean inter-rater agreement ranged between 0.96 and 1 at the subtest level (e.g. vocabulary in WAIS-IV at first assessment) and from 0.88 to 1 for individual test items (e.g. figure A in the VR I subtest at first assessment). All discrepancies were resolved between the two coders, and the resolved scorings were used for analyses.

Results

First assessment

The first neuropsychological assessment showed that SN's overall intellectual ability was in the above-average range [full-scale intelligence quotient (FSIQ) = 117], with particularly high scores in verbal comprehension (see Table 1). No impairments were observed in speech production, language comprehension, basic motor or visuoconstructive function. Her performance was well below the expected level for estimated premorbid abilities in several other cognitive domains, however. As shown in Tables 1 and 2, SN's visuomotor abilities were unexpectedly slow and her perceptual reasoning unexpectedly low relative to her high levels of academic and professional achievement and verbal abilities.

While SN's verbal memory was not impaired, her visual memory scores were lower than expected, especially when recall was delayed (see Table 1). Consistent with this pattern, she scored in the impaired range on the Rey-Osterrieth Complex Figure task when drawing from memory, but her performance was intact on the direct copy task. Together, these results suggest a selective impairment in visual memory, especially when recall was delayed rather than immediate.

Thus, relative to SN's otherwise intact cognitive abilities, and to her background of high academic and professional achievement, her performance was slowed in visuomotor processing, and well below the expected level in perceptual reasoning and delayed visual memory. While her cognitive profile may not have been premorbidly uniform across all domains, the degree of discrepancy, together with her background, suggests a pattern of acquired and selective deficits.

Second assessment

At second assessment, SN's cognitive performance had noticeably improved across several domains (see Tables 1 and 2). The greatest improvements were seen in visuomotor speed and perceptual reasoning, the functions that had previously shown the greatest degree of impairment.

Importantly, these changes were greater than those typically seen because of practice effects. Average practice effects range typically from one-half to one-third of a standard deviation on the WAIS-IV.[53,54] SN's scores on the processing speed index (PSI), perceptual reasoning index (PRI), and working memory index (WMI) increased by 14, 12 and 6 points, improvements 150, 170 and 200% greater, respectively, than average practice effects in healthy participants in her age group over a 5-week test–retest interval. Her improvement on the Coding subtest, for example, was 400% greater relative to healthy adults in her age group over a 5-week test–retest interval, despite a much longer test–retest interval.

SN's memory performance also improved in the domains with below-expected scores at first assessment. While the improvement in visual immediate memory (as assessed by the Visual Immediate Memory Index) is probably not sufficiently large to reflect a meaningful change, the change in visual delayed memory very likely is: the observed change on the Visual Delayed Memory Index is greater than the 90% confidence interval for measurement error in all of the three clinical groups for which Iverson provided estimates,[53] suggesting that the difference likely reflects real and meaningful improvement.

Despite these improvements, subtest scores suggest that SN's visual memory did not recover to the expected premorbid level. Relative to the mean scaled score (=15) for the eight administered primary subtests, SN's scaled scores were still unusually low on the FP I and II subtests ($p < 0.05$ and $p < 0.01$, respectively).[55] The difference between the mean scaled score and her VR II score was also equally large, suggesting that the level of performance was abnormally low also on this subtest (4). Together, these results suggest that SN's delayed visual memory was still below expected at second assessment.

Discussion

We presented a case of cognitive dysfunction that developed during long-term polypharmacy in a patient who had received a bipolar disorder diagnosis. Our patient, SN, a 41-year-old woman with a doctoral degree and a successful professional career, gradually became forgetful, visually distractible, and unable to function in her normal occupational and social roles after taking lithium for several months at a commonly used dosage, in combination with other psychiatric drugs she had taken as prescribed for years.

The first neuropsychological assessment, conducted when SN was still maintained on all psychiatric drugs, showed that SN's performance was well below the expected level in tasks requiring visuomotor speed, visual processing, and delayed visual memory. In contrast, her verbal intellectual abilities and verbal memory were largely intact, with performance at above-average or ceiling levels. The second evaluation, conducted 23–29 months after psychiatric medications were withdrawn, showed that the cognitive deficits had improved substantially, albeit not completely. Importantly, SN was able to return to work and resume her normal social functions soon after the discontinuation of her psychiatric drugs, providing an important real-life outcome reference for the neuropsychological test results.

SN's cognitive difficulties emerged over a period of several months after lithium was initiated, strongly suggesting lithium as the likely primary etiological factor. This possibility is further supported by experimental evidence demonstrating that lithium impairs performance in several cognitive domains, including visuomotor speed and visual memory.[11,12,42,43,56] Contrary to common views in psychiatry,[23] our case shows that conditions of cognitive impairment involving lithium do not necessarily occur in the context of full-on intoxication. It is, however, an open question whether SN's condition was caused by lithium alone or by a combination of lithium and other drugs. In addition to lithium and antipsychotics, benzodiazepines[57] and zopiclone[58] are also known to affect cognition.

While neuropsychological indices of visuomotor processing speed and visual memory are generally sensitive to various forms of organic brain disorder,[59] the findings are congruous with studies reporting associations between long-term lithium treatment and impaired visual cognition and memory in psychiatric patients.[10,60–64] SN experienced significant problems in her social and occupational life, which is consistent with evidence associating

neuropsychological impairment with poorer psychosocial functioning in bipolar disorder.[65,66]

Our case demonstrates that psychiatric polypharmacy can be associated with patterns of domain-specific cognitive dysfunction, and that cognitive abilities can recover, at least in part, after psychiatric drugs are discontinued. That SN was able to return to work and resume her normal social roles after psychiatric drugs were withdrawn suggests, together with her improved neuropsychological testing results, that further research into the cognitive benefits of deprescribing is warranted in psychiatry. In SN's case, the benefits of discontinuing the psychiatric treatments certainly outweighed the harms.

Despite recommendations for moving toward more evidence-based prescribing,[3,67] patients with a bipolar diagnosis are commonly prescribed combinations of psychiatric drugs, often against recommendations and scientific evidence.[9,68] Evidence indicates that the use of psychiatric polypharmacy is frequently influenced by factors other than a careful consideration of evidence regarding benefits and harms.[69] Evidence also suggests that a vast number of patients receive a bipolar diagnosis when it is not appropriate,[70] which was likely true in SN's case also. Recent initiatives have underscored the potential advantages of deprescribing,[6,71] and of avoiding overtreatment and overdiagnosis.[49] In light of our case, these efforts seem recommendable.

More specifically, our case calls into question whether the risks of cognitive impairment are adequately recognized in the treatment of patients with a bipolar diagnosis. SN's case is at odds with clinical practice guidelines that maintain that the risk of cognitive impairment is trivial.[23] In contrast, the case supports the opposite recommendation that patients undergoing lithium treatment be carefully monitored for signs of cognitive impairment even at commonly used dosages, a position taken by some, but not all, guidelines.[72] Future studies could perhaps shed further light on the risks of impairment by including results of drug plasma concentration in combination with tests of cognitive function.

The number of drugs is generally the single best predictor of adverse events.[6] If neurological problems in psychiatric patients emerge, however, the problems are often attributed to the psychiatric illness. Clinical practice guidelines in psychiatry commonly conjecture that the cognitive problems that many bipolar patients experience 'may be a quasi-toxic consequence of the intensity of the illness course,' rather than a potential risk of the psychopharmacological treatments often prescribed in combinations.[46] Conditions of subacute cognitive dysfunction may thus remain undetected, unreported, and misdiagnosed even if patients do recognize them and bring them up.

As in several other documented cases involving lithium (in combination or in the absence of other psychopharmacological agents), SN's condition developed gradually over months of exposure at a recommended dosage, went unnoticed at first, and was repeatedly clinically misinterpreted. The psychiatrist who had initiated the treatment, the clinical team to whom SN was referred, and the neurologist who examined her all failed to suspect that SN's difficulties were related to her psychiatric medication. SN had not been informed of the risk of adverse cognitive effects when consenting to treatment, and she did not know to associate the subjective feelings of cognitive slowing to the medication, although the experience is common among patients and healthy subjects taking lithium.[73] Her case is unfortunately not an isolated incident: in one previous case, three neurologists and a neuropsychologist all similarly misdiagnosed the patient's cognitive impairment until lithium was withdrawn coincidentally and the patient improved.[34] In yet a third case, the patient suffered from a debilitating lithium-induced cognitive impairment for 2 years because the deficits were misdiagnosed as dementia.[37] The condition resolved after the drug was withdrawn, as in SN's case.

More generally, our case underscores the need for more rigorous research efforts to understand the effects of psychiatric drugs and their discontinuation on brain and cognition especially over the long term. In the case of lithium, a large part of the published research speaks to its short-term cognitive effects only. Longer-term studies, in contrast, are few and frequently suffer from methodological problems.[10,56] Thus, there is a need for rigorously designed studies that can take the possibility of individual variability and heterogeneous outcomes into consideration, in addition to the need for a better understanding of the benefits and risks of psychiatric drug discontinuation in general.

Patient perspective

SN describes her experience:

> 'A sudden decline in cognitive performance is a life-shattering tragedy for an active academic and a mother of two. When prescribed lithium, I wasn't informed of any risks of developing cognitive problems, nor was there any follow up focused on these side effects.'
>
> 'I experienced severe memory problems. I wasn't able to memorize the appointments in my calendar, and I started missing important meetings with clients and family. Using my bank account digitally became very difficult since I repeatedly mistyped the number codes. My speech slowed down. I was overtaken by a brain fog that had no obvious reason. This worried me and my family deeply and I wasn't able to continue in my work. A brain scan was done, but no tumors or changes were found.'
>
> 'My psychiatrists and general practitioners were unable to diagnose the cause of my sudden neurological problems. Luckily, I saw a neuropsychologist who suggested that my symptoms could be lithium-related. After tapering off psychiatric drugs, which was my own decision and done under professional supervision, my wellbeing improved quickly and I was able to return to my previous work and lifestyle. After quitting lithium and other medications, I haven't had any psychiatric symptoms that would essentially distract me from my work or family life.'
>
> 'Getting off SSRI medication, lithium and quetiapine was a quick process for me, although I didn't stop them at once but tapered the doses down gradually during a few months. I wasn't informed on the possible side effects of stopping the medication by my doctor. During the process, I had restless legs, difficulties sleeping and sudden sensations that resembled electric shocks in my brain. The shock symptoms were already familiar to me from my two earlier experiences of stopping SSRI medication. I also noticed a significant change in my sleep pattern. While being on medication, I had difficulties waking up and I felt sleepy until noon, but without medication I started waking up early feeling refreshed. Most symptoms faded away with time, with the exception of restless legs that still bother me occasionally.'

Authors' Note

Jussi Valtonen is now affiliated to Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Finland. This research was presented at the scientific meeting of the Federation of the European Societies of Neuropsychology in Milan, 5–7 September 2019.

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Notes

(1) The Social Insurance Institution KELA in Finland requires that all patients undergo an independent psychiatric evaluation and receive a diagnosis for psychotherapy to be publicly reimbursed. The clinical psychiatric evaluation SN underwent in September 2008 was conducted for this reason alone, as opposed to subjective complaints of elevated mood. Having experienced difficulties in her marriage and stress at work, SN wanted to return to psychotherapy. While KELA's requirement of psychiatric evaluations sounds reasonable per se, evidence suggests that assessments conducted in the absence of clinical complaints may increase the risk of overdiagnosis and lead to unnecessary interventions.[49,74,75] SN seems a potential case example of this pattern, especially in light of the increases in the diagnoses of bipolar disorder.[70,76,77]

(2) Because Matrices had not been conducted at first assessment, they were also not used to calculate intelligence quotient (IQ) indexes at second assessment for consistency.

(3) Rey-Osterreith Complex Figure;[78] Verbal Fluency;[80] and the Finger Tapping Test.[81] For Phonemic Fluency, only two items (words beginning with the letters 'k' and 's') were administered, corresponding to common protocol in Finland. For comparison with American norms collected using three items, we transposed the sum of SN's scores by multiplying by 1.5. While this could be problematic in cases with large inter-item differences in performance,

SN's performance was numerically identical on both administered items, suggesting that the results are reasonably robust. The results from Verbal Fluency tests should be interpreted with caution, however, as they were conducted in Finnish.

(4) Ryan et al.[55] do not provide norms for VR II, but an identical discrepancy would be significant at the 0.05 level on most of the other subtests.

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