Impulsivity is an important feature of many mental health disorders, including Alzheimer’s disease (AD) and related dementias. Impulsive behaviours in AD pose significant management problems for caregivers, and may contribute to risk of injury in both patients and caregivers. While impulsive behaviours likely are contributed to by multiple factors, dysfunction of the brain’s inhibiting system is one of the most significant causes.

Disinhibition is seen with lesions involving the limbic system, anterior basal ganglia, and orbital frontal cortex. These structures form a system which is mediated, at least in part, by the neurotransmitter serotonin. Low serotonin has been correlated with “irritable and impulsive aggression” in animals and across a broad range of diagnostic groups.

A deficit in the serotonin system has been demonstrated in AD. Disruption of the system may lead to impulsive behaviour in the behavioural realm, affective lability and irritability in the affective realm, and rapid, poorly planned responses in the cognitive realm. This paper reviews the assessment, prevalence and pharmacologic management of disinhibition in AD.

Phenomenology and Assessment

Historically, the assessment of disinhibition was limited primarily to the behavioural realm, using instruments such as the Buss-Durkee Hostility Inventory (BDHI) and the Barratt Impulsivity Scale-10th revision (BIS-10). More recently, the Neuropsychiatric Inventory (NPI) has been widely used in research related to the dementias. The NPI assesses 12 affective and behavioural realms commonly disturbed in neuropsychiatric populations. Disinhibition is assessed primarily by the NPI in the subscales of “disinhibition” and “irritability/lability.”

The screening questions for these subscales provide a reasonable clinical definition of disinhibition, and provide clinicians with a measurement tool that is quick to administer and has good reliability and validity. The NPI questions for disinhibition include: “Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things

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that are embarrassing to you or others?"

The NPI screening questions for irritability/lability include: “Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient?” These questions do not refer to frustration over memory loss or inability to perform usual tasks; instead, they are concerned with whether the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

Examples of behaviours in these realms are also contained in the NPI, including: “Does the patient take liberties or touch others in a way that is out of character for him/her?” and “Does the patient have sudden flashes of anger?”

The NPI also provides measures of the frequency and severity of behaviours, as well as an assessment of the impact of these behaviours on the caregiver. Clearly, these factors, among others (e.g., safety), will be important in determining the need for intervention and also should be considered in assessing the response to any intervention provided.

Since the behavioural changes in patients with AD may have multifactorial origins, the assessment of disinhibition warrants a thorough work-up for potentially treatable causes.

Prevalence
As assessed by the NPI, the point prevalence of disinhibition in AD has been found to range from 9.1% (in a community sample)\(^9\) to 36% (in an outpatient sample).\(^{10}\) Another outpatient AD sample demonstrated a point prevalence of disinhibition of greater than 20%,\(^1\) which compared to a rate of greater than 70% in patients with frontotemporal dementia (FTD).

Nondemented seniors in the community were found to have a disinhibition rate of only 0.9%, as assessed by the NPI.\(^9\)

With regards to the point prevalence of irritability/lability in AD, the NPI rates range from 20.4% (in a community sample)\(^9\) to over 40% (outpatient samples).\(^{10,11}\)

Even higher rates of disinhibition have been reported using non-structured assessments. Haupt\(^12\) found that 74% of mildly to moderately impaired patients with AD demonstrated lability, while 41% demonstrated “intrusiveness.”

With its impact on impulsive behaviour, affective lability and irritability, disinhibition clearly is a common problem in AD and other dementing illnesses.

Pharmacologic Management
At present, most patients with AD are potential candidates for a trial with an acetylcholinesterase inhibitor, such as donepezil or galantamine. The current primary indication for these compounds is the symptomatic treatment of cognitive impairment in mild to moderate AD. Changes in behaviour are increasingly being reported with these compounds, suggesting that they also be considered for the indication of treating certain behavioural changes seen in AD.

In a retrospective study of 30 AD patients treated with donepezil, a positive response to the medication was predicted by the presence of pretreatment irritability and disinhibition, as assessed by the NPI.\(^{13}\) This study also preliminarily assessed these patients’ response to donepezil in terms of disinhibition and irritability/lability; improvements were felt to have occurred with treatment. This study was not a randomized clinical trial (RCT). However, in conjunction with the increasing evidence from RCTs of acetylcholinesterase inhibitors which have assessed changes in...
behaviour as an outcome variable (e.g., Feldman et al\textsuperscript{14}), there is a probability that these compounds may exert a beneficial effect on disinhibition and irritability/lability in AD. Therefore, if an AD patient with cognitive impairment is being considered for such a trial, it would appear reasonable to initiate pharmacologic management with an acetylcholinesterase inhibitor if disinhibition, irritability and lability are present.

Some patients will not tolerate acetylcholinesterase inhibitors or, for other reasons, may not be considered for such a trial. In other patients, problems with disinhibition persist, despite treatment with an acetylcholinesterase inhibitor. For these patients, alternative medication strategies may need to be considered.

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At present, antipsychotics are the medications being used most frequently for the behavioural disturbances of AD. However, the efficacy of these antipsychotics is fairly low versus placebo response rates.\textsuperscript{15,16} There also are significant potential risks with these compounds. Furthermore, considering “general behaviour” as the target for pharmacologic interventions—without further specifying the nature (and, hence, underlying mechanisms) of the behaviour—does not allow for targeting of specific medications to specific behaviours. Being more specific may allow for improved efficacy and safety in the pharmacologic management of the general behaviours of AD, and in the specific management of disinhibition.

Selective serotonin reuptake inhibitors (SSRIs) have been considered as potential treatments for disinhibited behaviours and effects in AD, and are generally considered safer than antipsychotics for patients with dementia. For example, sertraline, a commonly used SSRI, was reported to decrease irritability and aggression in two patients with Huntington’s Chorea;\textsuperscript{17} and in an RCT of the SSRI citalopram, patients with AD improved in terms of showing less irritability versus those receiving placebo.\textsuperscript{18} This improvement did not occur in the patients with vascular dementia.

In an RCT of fluvoxamine, trend level improvements in irritability were seen in a group of patients with AD and multi-infarct dementia.\textsuperscript{19}

Last but not least, in an open-label study of fluoxetine, sertraline or paroxetine, over half of 11 subjects with FTD exhibited a decline in disinhibition over a three-month treatment period.\textsuperscript{20}

The above results are promising early findings that warrant and require further study. However, additional support for the possible use of SSRIs also can be derived from studies in nondemented populations on response to treatment of disinhibition. For example, fluoxetine was reported to have led to a decrease in impulsive aggression in two patients with antisocial personality disorder and in one patient with borderline personality disorder (BPD).\textsuperscript{21} Similarly, irritability and overt aggression were reported to have decreased in an open-label study of personality disordered patients (81 of whom were diagnosed with BPD) using sertraline.\textsuperscript{22}

In an RCT on SSRI treatment for major depression (using sertraline or citalopram), the rate of comorbid BPD was found to drop from 20% at baseline to 10% with treatment.\textsuperscript{23}

An RCT\textsuperscript{24} of paroxetine showed a reduction in anger and suicide attempts in recurrent “suiciders” who did not have an Axis I disorder (most were diagnosed with a personality disorder). Paroxetine has been shown to reduce hostility and negative affects in healthy volunteers.\textsuperscript{25}

Citalopram also has been shown to decrease aggression in chronically violent patients with schizophrenia.\textsuperscript{26}

Finally, there is suggestive, but mixed, evidence of efficacy for SSRIs in treating substance-abuse disorders.\textsuperscript{27}

While these studies are not direct evidence of efficacy in the treatment of disinhibition in AD, they do provide ancillary evidence in support of the possibility that SSRIs may be helpful for disinhibition in AD and related dementias.

Summary

Disinhibition is caused, partly, by dysfunction of an orbital-frontal-subcortical system which, itself, is partly mediated by the neurotrans-
mmitter serotonin. Dysfunction of this system may occur in the dementias and, hence, impulsive behaviours and affective lability/irritability are commonly seen. If indicated by frequent, severe, disruptive or dangerous disinhibition, pharmacologic management may include a trial with an acetylcholinesterase inhibitor, if such a compound is otherwise being considered (i.e., typically for the indication of symptomatic treatment).

If an acetylcholinesterase inhibitor is not being considered, or if one already is being used without full benefit with regards to the disinhibition, a trial with an SSRI could be considered. However, the evidence in support of this recommendation is preliminary. Therefore, careful monitoring of response, and for adverse effects (e.g., inducing mania, insomnia), needs to be undertaken. Our clinical experience has been that higher doses of SSRIs sometimes are needed, although this type of observation does not replace systematic research. As such, SSRI trials should start with a low dose and be titrated slowly upwards—only if needed and only if tolerated. Further research is strongly supported by the existing data.

References: