BPSD and the Psychosis of AD: Treatment Possibilities

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Purpose: "Can we identify appropriate clinical entities or targets of drug development in this area?"

I would like to begin by congratulating the FDA for giving considered and thoughtful attention to this very important public health problem.

AD is the major form of dementing disorder and its also the best understood. Therefore in addressing the question, "Can we identify appropriate clinical entities or targets of drug development in this area?", it is useful to focus on AD.

In focusing on AD, it is also useful to note that conclusions for AD will frequently apply to other dementing entities. For example, cerebrovascular dementia consists primarily of patients with AD and notable concomitant cerebrovascular disease (mixed dementia). Also, cerebrovascular disease is now believed to represent a continuum of relevance for AD as well as for cerebrovascular dementia. [1-6] Similarly, Lewy body dementia is frequently noted to be accompanied by AD neuropathologic concomitants, and is sometimes seen to be a Lewy body variant of AD.[7]

In comparison with other major psychiatric disorders, much is known about AD. For example, AD is known to be accompanied by brain changes. These include: (a) accumulation of tau positive paired helical filaments in neurons of the neocortex; (b) accumulation of amyloid plaques in the neocortex comprised in part, of the ß-amyloid protein; (c) cellular and volume losses in the hippocampus and to some extent in other brain structures. Clinically, AD is recognized to be a progressive disorder with linear declines in cognition and functioning extending over a period of up to approximately 20 years.

AD has also long been know to be accompanied by "Behavioral and Psychological Symptoms" (BPSD), including psychotic symptoms.[8-10] For example, in Alois Alzheimer's classic case description, he noted BPSD in approximately half of his clinical description.[8] He noted, in part, that his patient believed "that people were out to murder her", seems to have auditory hallucinations", "dragged objects here and there and hid them", and that "often she screams for many hours in a horrible voice." Therefore, Alzheimer identified delusions, hallucinations, activity disturbances, and aggressivity, as part of the clinical presentation in his classic case.

Frequently, BPSD in AD are: (1) disturbing to family members or other caregivers, and /or, (2) dangerous and/or distressful to the AD patient.

In these cases where BPSD are disturbing, distressful, or dangerous, physicians often endeavor to treat these symptoms with psychotropic medications.

This has been true for decades and psychotropic medications are among the most frequently prescribed medications for AD and other dementing disorders.

Psychotropics appear to be prescribed for more than ½ of all patients diagnosed with AD at any given time, and are prescribed at some point in the course of AD for the great majority of AD patients. The kinds of psychotropics prescribed for disturbing, distressful, or dangerous BPSD symptoms are quite diverse. Doctors prescribe antipsychotic medications, antidepressant medications, anxiolytic agents, mood stabilizers and antimanic agents, including anticonvulsants, sedating medications, other substances and various combinations of these medications and classes of medications. However, in the absence of appropriate studies, doctors have had little information to guide them as to: (1) what BPSD symptoms

respond to pharmacologic intervention?; (2) what medications should be prescribed for these symptoms?; and (3) what are the side effects of treatment in the context of AD and other dementias?

In endeavoring to treat disturbing, distressful, and/or dangerous BPSD with medications, physicians have not had any illusions that they are treating the underlying, fundamental disease process. Physicians have been aware that in treating these BPSD with medications: they may not be affecting the dementia patient's cognition; or, they may be worsening the dementia patient's cognition; or, conceivably, they may be improving the dementia patient's cognition. Similarly, physicians have been aware that in treating BPSD symptoms with medications, they may not be affecting the dementia patient's functioning; or, they may be worsening the dementia patient's functioning; or, conceivably, they may be improving the dementia patient's functioning.

Clinicians have also understood that worsening in cognition and/or functioning, could be the result of side effects of potential BPSD treatments.

For these, and other reasons, there has been a need to separate BPSD which may respond to psychotropic intervention, from cognitive and functional symptoms of dementia.

What BPSD respond to pharmacologic intervention?

Initial studies nearly 15 years ago indicated that seven broad categories of BPSD which appear to be responsive to intervention with the antipsychotic medication thioridazine can be identified.[11, 12] These categories of BPSD which are potentially responsive to antipsychotic medications are as follows: (A) paranoid and delusional ideation; (B) hallucinations; (C) activity disturbances; (D) aggressivity; (E) diurnal (sleep) rhythm disturbances; (F) affective disturbances; and, (G) anxieties and phobias.

Studies also indicated that the nature of these BPSD symptoms in AD is very different from the nature of these symptoms in other mental disorders. Consequently, although the categories of BPSD symptoms in dementia are superficially similar to the categories of symptoms in, for example, the psychosis of schizophrenia or in the depression of major affective disorder, the specific nature of these symptoms in AD and related dementias are in all cases different.

These unique features appear to be the result of:

(1) the special psychological factors operating in AD and related dementias and,

(2) the special neurochemical milieu of AD and related dementias.

Psychologically, progressive cognitive and functional losses in dementia influence the nature of BPSD. Neurochemically, it is clear that nature of cholinergeric, dopaminergic, noradrenergic and other, neurotransmitter and neurochemical changes in AD are different from the neurochemical changes and background in schizophrenia or major depression. These unique psychological and neurochemical features would naturally be expected to produce a unique phenomenology. Studies have indicated that this is indeed the case.

The progression of these BPSD symptoms is different from the progression of cognitive and functional changes in AD. Cognitive and functional changes in AD worsen progressively throughout the course of the disease. This progressive worsening of cognitive and functional changes in AD appears to occur in a linear fashion with the progression of AD.

In contrast, the BPSD symptoms which are potentially responsive to anti-psychotic medications, which can be called the "Psychosis of AD and Related Dementias" or, more briefly, the "Psychosis of AD",

consists of symptoms which all peak in occurrence at some point prior to the final stage of AD. [13]

Sometimes it is hypothesized that these Psychosis of AD Symptoms decrease in severe dementia because the patient can no longer articulate the symptoms. However, this clearly would not explain why sleep disturbances peak in moderate AD, or why aggressivity appears to peak well before patients lose speech capacity when patients are still mobile and capable of aggressive physical and other outbursts.

It should also be noted that BPSD is a broad category which includes many symptoms which do not fall within the "Psychosis of AD Syndrome." For example, patients with dementia develop the so-called, "mirror sign", wherein patients no longer recognize their image in the mirror and they will therefore speak to their image in the mirror. This is not a BPSD symptom which is likely to respond to antipsychotic or related medications. Therefore, the mirror sign has not been hypothesized to fall within the Psychosis of AD. Similarly, patients with dementia frequently show weight loss, especially very late in the disease. This is probably related to rigidity, inactivity, and other factors. This weight change is not a BPSD symptom within the Psychosis of AD Syndrome.

Early in the course of dementia, patients commonly withdraw. This withdrawal, commonly termed "apathy", appears to be a psychological symptom related to the patient's decreased competence. Since they don't understand what is being said, the patient keeps quiet. This apathy is not a BPSD symptom within the Psychosis of AD Syndrome.

When symptoms do fall within the Psychosis of AD, the extent to which symptoms are disturbing, distressful, and/or dangerous, is related to the need for treatment and the magnitude of symptomatology. For example, if a patient mistakes their spouse for their mother, but accepts their spouse as their spouse

when corrected, then this misidentification is not a Psychosis of AD symptom. However, if the patient insists that the spouse is not their spouse, then this **is** a Psychosis of AD symptom. If the patient becomes angry at their spouse for being an imposter, then this symptom is more disturbing. If the patient becomes violent with their spouse because of the belief that they are an imposter, then the symptom is still more disturbing.

In 1987, we developed a rating instrument, the BEHAVE-AD, which measures, the 7 categories of symptoms in the Psychosis of AD, and measures 25 generally characteristic symptoms in these 7 categories, and rates each of these symptoms on a 4-point severity scale.

The BEHAVE-AD also contains a global assessment of the degree to which these Psychosis of AD Symptoms are troubling to the caregiver and/or dangerous to the patient.

Initial studies, as already noted, indicated that the BEHAVE-AD symptoms and symptom categories: (1) were responsive to neuroleptic intervention; (2) were important in AD. Subsequent studies indicated that the reliability of the BEHAVE-AD is excellent and similar to that of the most reliable cognitive dementia assessments. [14-16]

A recently published multi-center trial has indicated that each of the BEHAVE-AD symptomatic categories responds statistically significantly to even minimal, non-specific psychological support. [17] In response to the psychological effects associated with being in a trial and being on placebo treatment, total BEHAVE-AD scores decreased by 25%. Furthermore, each of the 7 BEHAVE-AD symptomatic category scores decreased by 18% to 45%. In this trial, the best dose of an anti-psychotic medication produced a decrease in total BEHAVE-AD scores of approximately 40%. Differences between the

placebo treatment group and the neuroleptic treatment group in BEHAVE-AD total scores were statistically significant.

Categories of BEHAVE-AD symptoms which differed between the placebo and neuroleptic treatment groups at end point by > 10% included: (1) paranoid and delusional ideation; (2) activity disturbances; (3) aggressivity; and (4) diurnal rhythm disturbance.

All these differences were in favor of the neuroleptic intervention.

Importantly, all these symptomatic changes on placebo and neuroleptic treatment in BEHAVE-AD scores appeared to occur independently of cognitive or functional effects of the intervention.

In summary a Psychosis of AD Syndrome is identifiable. This syndrome appears to have both psychologic and neurochemical origins. Accordingly, the syndrome responds to both psychologic and neurochemical treatment.

Rating scales have been developed which can measure this syndrome reliably and sensitively on clinically meaningful parameters.

It is important to note that the Psychotic BPSD Syndrome is more than simply delusions, hallucinations, and aggressivity, or even dementia specific, delusions, hallucinations, and aggressivity.

The BPRS, used to assess the efficacy of antipsychotic medications for schizophrenia, includes various associated symptoms. Among these associated symptoms are: somatic concerns; anxiety; emotional withdrawal; etc. These associated symptoms are assessed in addition to: suspiciousness; hallucinatory behaviors; and uncooperativeness. [18] Similarly the Hamilton Depression Scale includes: somatic anxiety; somatic gastrointestinal symptoms; genital symptoms; hypochondriasis; weight loss; insight,

etc. There are all assessed in addition to depressed mood, feelings of guilt; and suicidal ideation. [19] Similarly, the scales used to measure the Psychosis of AD should include associated symptomatology.

The Psychosis of AD is potentially independent of the cognitive and functional changes in dementia. Furthermore, the Psychosis of AD can potentially be measured independently of the cognitive and functional changes in dementia. In the interest of accurate assessment, the Psychosis of AD should be assessed independently of the cognitive and functional symptoms of dementia.

Because the etiopathogenesis, and the phenomenologic manifestation, and the symptomatic background, of the Psychosis of AD is very different from the psychosis of schizophrenia, and because, treatment and side effect issues are different, it is important to study the Psychosis of AD independently. Because of the prevalence and morbidity associated with Psychosis of AD it is important that these issues be investigated pharmacologically. Appropriate methodologies are available for the investigation of these issues.

The Psychosis of AD is an appropriate area for drug development and regulation at the present time.

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