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Neuropsychiatric symptoms in Alzheimer's disease

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Abstract

Neuropsychiatric symptoms (NPS) are core features of Alzheimer's disease and related dementias. Once thought to emerge primarily in people with late-stage disease, these symptoms are currently known to manifest commonly in very early disease and in prodromal phases, such as mild cognitive impairment. Despite decades of research, reliable treatments for dementia-associated NPS have not been found, and those that are in widespread use present notable risks for people using these medications. An Alzheimer's Association Research Roundtable was convened in the spring of 2010 to review what is known about NPS in Alzheimer's disease, to discuss classification and underlying neuropathogenesis and vulnerabilities, and to formulate recommendations for new approaches to tailored therapeutics.

Keywords

Geriatric neuropsychiatric symptoms; Alzheimer's disease; Mild cognitive impairment; Neuropsychiatric symptom management; Executive dysfunction syndrome

1. Introduction

Although Alzheimer's disease (AD) is usually considered a cognitive disorder, almost all people diagnosed with AD develop neuropsychiatric symptoms (NPS) at some stage during their disease. Population-based studies show that the frequency of NPS is much higher in people with AD and mild cognitive impairment (MCI) than in the general population [1,2]. Of all the NPS, depression and apathy are the most frequently observed symptoms in people with MCI and early AD, although the incidence of verbal and physical agitation is also high

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across all stages of MCI and AD. As the disease progresses, delusions, hallucinations, and aggression become more common, whereas apathy is the most persistent and frequent NPS throughout all the stages of AD. Additionally, circadian sleep-wake rhythms become exaggerated as compared with the phase shifts associated with normal aging. The prognostic significance of NPS in the dementing process of AD should not be underestimated. People with MCI progress to AD at a much higher rate if they have depression, whereas those with mild behavioral impairment are more likely to develop dementia even if they have normal cognition [3], and agitation, apathy, anxiety, disinhibition, euphoria, and irritability may have stronger associations with incident MCI than depression [4].

NPS are also associated with major adverse effects on daily function, quality of life, and reduced time to institutionalization. Therefore, NPS also have a major adverse effect on caregivers [5].

How should NPS be identified, classified, and treated? Because individual NPS often cluster together and may overlap across symptom clusters, it has been challenging to delineate clear syndromes. However, across different populations and using factor and cluster analytic methods, several syndromes appear fairly consistently and deserve further research. These most often include depression, psychosis, apathy, hyperactivity/agitation, sleep disorders, and prefrontal syndromes. It is important to gain more clarity regarding these syndromes because their phenotype may help to delineate the underlying neural regions and circuitry, and thereby shed light on neuropathogenesis. Consequently, insight into the neuropathogenesis, which may be distinct from the brain regions underlying language and memory deficits of AD, can be gained. Whether some persons are more susceptible to exhibit certain NPS related to their genetics, medical comorbidities, or lifestyle choices, or whether these are more related to the level of involvement of certain neurotransmitter systems or anterior (e.g., frontolimbic) brain regional atrophy and disconnection is unknown. Limited translational research into NPS suggests that all of the above may play a role. Further understanding of these biological underpinnings offers an opportunity to develop more targeted drug treatments and nonpharmacological management techniques that enhance caregiver coping skills. The focus of this article is on the translational biological parameters that could assist in understanding and treating NPS syndromes of AD and MCI.

2. Phenotype measurement

With the exception of “Psychosis of AD” [6] and “Depression of AD” [7,8], there are few consensus diagnostic criteria for NPS in dementia. Ensuring that these symptoms occur specifically in the context of the AD process is important to distinguish them from other causes such as comorbid or preexisting psychiatric disorders. There are also numerous methodological issues to consider when evaluating NPS in the context of dementia, including participant population (controls, MCI, or AD), study duration, frequency of assessment, desired outcome of a particular study (symptom reduction, secondary prevention/delayed onset of psychopathology, or primary prevention), and use of informants (which can introduce bias). Validated scales in widespread use fall into two categories: focused scales—for example, scales for depression or agitation—and general scales, including the Neuropsychiatric Inventory (NPI), that assess more than one NPS domain [9]. In general, the type of instruments used depends on the specific study objectives.

Although the NPI is the most widely used NPS measure, it has some drawbacks. Subscales that have not yet been validated are commonly used in studies. Also, it is based on caregiver input obtained during a clinical interview and does not allow the clinician’s judgment to be factored into the assessment. The Neuropsychiatric Inventory Clinician (NPI-C) Rating was developed in part to address such shortcomings. It is based on observable and behavioral

data and is specific to people with dementia [10]. The NPI-C was developed after a comprehensive review of 19 existing NPS measures that produced new NPI items sorted into existing NPI domains. Aberrant vocalization was added as a new domain, whereas the agitation/aggression domain of the original NPI was split to arrive at a total of 14 domains for the NPI-C [11]. Unlike the NPI, each domain and potentially each subquestion within a domain can be rated on the NPI-C. Caregiver and patients rate frequency, severity, and distress of each item, and the clinician provides an overall rating based on interviews and additional chart information, which brings additional strength to the measure when compared with the original.

NPI-C was field tested in an international validation study and compared with focused scales to determine convergent validity. It was trimmed to 142 items (61 more than the NPI) and has been translated into several European languages [11]. The revised NPI-C can be used to rate single or multiple domains and maintains the main advantages of the NPI, including speed and ease of administration and the ability to compare across trials and sites.

3. Clinical phenomenology and pathophysiology

Delusions have been associated with an increase in muscarinic receptors in the orbitofrontal cortex. Fluorodeoxyglucose positron emission tomography (PET) analysis has revealed correlations between delusions and reduced glucose metabolism in the right frontal region of the brain [12]. Many challenges remain to identifying pathologic correlates, not least of which is the complication of the underlying neurodegeneration and the multiple pathologies and symptoms often seen in single cases. For example, poor insight increases the likelihood of delusions in persons with dementia. In fact, fluorodeoxyglucose PET studies suggest overlap between brain regions demonstrating reduced metabolism during episodes of delusions and poor insight. Altered glucose metabolism as measured by PET has also been associated with anxiety, apathy, agitation, and disinhibition in AD, with multiple brain regions involved [13–15]. The picture that emerges is that the underlying pathology for NPS is predominantly cortical. Although some symptoms can be linked to specific regions of the brain, others are associated with broader metabolic changes.

New PET imaging ligands for specific brain receptors might help to identify specific dysfunctional networks that contribute to individual NPS. For example, dopamine receptor availability is higher in people with AD/MCI who also have delusions and poor cholinergic binding, and is correlated with NPS, including blunted affect and emotional withdrawal [16]. Interestingly, in one study, cholinesterase inhibitor treatment increased metabolic rate and was associated with reduced NPS [17].

Many challenges exist to a better understanding of the pathology that underlies NPS. Future pathological studies require prospective assessment, larger numbers of volunteers, standardized assessments, and multimodal brain imaging analysis. There is a need to develop centers of excellence to examine NPS across all levels of discovery: etiology, pathogenesis, pathology, pathophysiology, and clinical disease. The overarching principles that are to be considered for studies of NPS in AD are course, context, and convergence: symptoms may change over the course of the disease (e.g., psychosis is more common in mid to late stages); symptoms may differ depending on the underlying cause (e.g., vascular damage, plaque burden, inflammation, tau pathology); and convergence may be important because the same symptoms or syndromes may be rooted in different pathophysiologies.

4. Classification and differentiation

There are two main clinical purposes to appropriately classify and characterize NPS in AD. One is to allow a diagnosis of AD versus other diseases. The second is to identify subgroups

of individuals with AD. NPS and their syndromes in AD can have phenotypic characteristics that help to distinguish them from other psychiatric disorders. For example, the types of delusional content or hallucinations differ from schizophrenia. Further, the symptom pattern may be differentiated to some degree from other types of dementias, for example, frontotemporal degeneration, in which euphoria is more common than in AD.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) III classified dementia as a primary diagnosis with subclassifications based on the presence of delirium or delusions [18]. It also noted that people may undergo personality changes, including becoming apathetic, withdrawn, paranoid, and/or irritable. DSM-IV also subclassified AD and other dementias based on behavior, including delirium, delusions, and behavior problems [19]. A text revision of DSM-IV listed AD as simply being with or without behavioral disturbance. DSM-V is currently being drafted and is due to be published in 2013. The current draft proposes two broad categories, tentatively named Major and Minor (or Mild) Neurocognitive Disorder. The “major” category will subsume dementias, including AD, vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and so forth. The “minor” (or mild) category will include neurocognitive impairment that does not reach the threshold of dementia and includes MCI of AD, as well as other disorders, not all necessarily progressive in nature. The DSM-V workgroup is currently discussing how to designate neuropsychiatric disturbances within this framework. Alternatives being discussed include specific subtypes of AD with various behavioral disturbances versus separate entities such as psychosis of AD (PAD) and depression of AD.

Two criteria that may help further classify NPS are central nervous system and peripheral biomarkers and genetic polymorphisms. At present, a range of ligands is available for imaging neurotransmitter receptors and assessing receptor occupancy in vivo. Molecular imaging of other psychiatric disorders, for example, schizophrenia and depression, suggests that receptor availability/occupancy alone cannot distinguish people with the disease from controls, but dynamic measures or interactions between measures may be informative [20]. For example, changes in glucose metabolism in response to treatment with antidepressants predict treatment outcome, as does an increase in serotonin transporter occupancy [21]. Going forward, it will be informative to look at biomarkers in nondemented controls and persons with MCI/AD with and without NPS. Biomarker analyses should also be combined with markers of drug response to understand the impact of NPS on dementia risk and progression.

Genotyping may help develop predictive models of who is at risk for NPS. Genetics may also help with nosology by shifting classification from phenomenology to etiology to help understand the latter. Currently, not much is known about the genetics of NPS in dementia, but association studies suggest that there is some degree of heritability in psychosis and depression [22,23]. Positive associations have been found for various neurotransmitter pathway genes, for example, although the data are often equivocal [24–26]. Going forward, large sample sizes of people with a diagnosis of AD who manifest NPS will be needed to identify genetic risk loci. It is likely that the genetic architecture of NPS in dementia will be polygenic with both common variants of small effect and rare variants of larger effect size.

5. NPS in prodromal AD

Several studies have reported that NPS are common in people diagnosed with MCI in a clinical setting [27]. More recently, data from the Mayo Clinic Study of Aging confirmed that the same is true for population-based samples. The study looked at >300 MCI cases and > 1500 controls, and found significant differences between MCI and controls on the presence of agitation, anxiety, apathy, delusions, depression, disinhibition, and irritability, as

judged by the NPI. In this setting, differences in apathy, anxiety, irritability, and depression most clearly distinguished between those with MCI from controls [2]. Additionally, Geda et al from Mayo Clinic Rochester conducted an exploratory analysis of the Alzheimer's Disease Neuroimaging Initiative (ADNI) data examining the correlations between the Neuropsychiatric Inventory–Questionnaire (NPI-Q) scores and Pittsburgh compound B (PiB) binding [28]. After adjusting for age, sex, and education, a weak correlation was found between Global ^{11}C-PiB-PET retention and total NPI-Q scores (r = 0.23 [0.03–0.41]), but significance was lost after adjusting for Mini-Mental State Examination (r = 0.13 [−0.07 to 0.320]) [29]. Similarly, there were weak correlations between regional ^{11}C-PiB-PET retentions (prefrontal, temporal, and parietal) and total NPI scores that dissipated when adjusting for the Mini-Mental State Exam.

Longitudinal incidence and interventional studies could address whether normal elderly persons with NPS are more at risk for developing MCI and whether treating those symptoms might prevent or delay progression to MCI and dementia. Several studies have addressed the impact of NPS on progression to dementia in persons diagnosed with MCI and in controls [30,31]. Although the results are mixed, there are indications that the presence of behavioral symptoms may increase the risk of dementia. These findings are supported by recent analysis of a much larger sample set from the National Alzheimer's Disease Coordinating Center database, which has more than 3600 participants diagnosed with MCI [32]. The data indicate that NPS, as judged by the NPI-Q, are associated with a higher risk of dementia in general, and also a higher risk for AD and frontotemporal degeneration. Specifically, in this MCI cohort, when delusions, agitation, and depression are noted on their respective NPI-Q subdomains, there is a more rapid progression to dementia.

Studying NPS in MCI could provide a basis for understanding how NPS change and evolve as dementia progresses. The Development of Screening Guidelines and Criteria for Predementia Alzheimer's disease study is a European collaborative to develop screening guidelines and clinical criteria for early diagnosis of AD [33]. It is a prospective, multicenter cohort study that has enrolled more than 800 subjects with MCI who were reassessed at 3-year follow-up postbaseline. Approximately 20% progressed to dementia. The data suggest that anxiety may be a risk factor for AD progression. Anxiety was also associated with abnormal cerebral spinal fluid levels of Aβ42 and total tau [34]. The data for other NPI domains were not as convincing; however, there are indications of interactions with comorbidities. In the Cognitive Function and Ageing Study in Britain, neither depression alone nor high blood pressure was a risk factor for dementia, but combining these variables was associated with a 2.5 increased risk for dementia [35]. Depression was also closely related to cognition in the Maastricht Aging Study, as were white matter lesions in a late-life depression cohort in Newcastle, UK. The data suggest that there may be an interaction between depression and vascular pathology in affecting cognitive decline and progression to dementia.

Other studies have shown that the combination of depression and/or apathy with diabetes increases risk for dementia. Incorporating the presence of depression, apathy, or other NPS into revised diagnostic criteria for AD is worth considering. Treating these symptoms might also delay progression of dementia. Psychotropic agents, for example, affect signaling pathways and may enhance neurotrophic and neuroprotective mechanisms in the brain. Although antipsychotic agents may not be the best choice because they have been found to be detrimental to some people with dementia, most antidepressants are relatively safe. Data also suggest that both galantamine and memantine treatment delay deterioration on the NPI total score and on specific NPI subdomains in people with cognitive impairment [36–39]. The data suggest that NPS may not only be risk factors but may also be markers of disease progression.

6. Efficacy trials and nonpharmacological approaches to NPS management

There is a long history of treatment for NPS in neurological conditions, starting with penicillin for encephalitis and culminating in the more recent atypical antipsychotic drugs. Many different treatments have been tested in dementia. Recent antipsychotic trials in dementia have followed a similar model, evaluating from 6 to 12 weeks of treatment with a placebo arm for comparison. They have all ended similarly, with, at best, a small improvement over placebo. Risperidone, for example, shows an improvement in psychosis in the Behavioral Pathology in Alzheimer's Disease Rating Scale [39], but only slightly more so than placebo. Other antipsychotics have similar outcomes or are negative. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease study [40] demonstrated that these drugs have little effect overall versus placebo. In fact, they are equally likely to harm people with dementia as to help them. The dementia antipsychotic withdrawal trial found no significant efficacy for drug versus placebo, thereby suggesting that people do not need to be maintained on antipsychotics [41].

Studies suggest that there are potential benefits from nonpharmacological treatment of NPS in dementia. Targeting environmental and underlying medical triggers may help to attenuate behavioral symptoms. There is good evidence, for example, that music can reduce agitation during bathing. Exercise and pleasant experiences can reduce depression, and activity can reduce the need for restraints in agitated persons. However, most such studies have been of short duration with small sample and effect sizes [42]. Larger randomized trials have found that family caregiver training can improve behavior in people with AD [43]. But how nonpharmacological treatment relates to pathology is still unclear. For example, people may suffer less stress because their capabilities have been realigned. There is a need to further study the relationships between dementia, dementia subtypes, and behavioral treatments.

7. Steps to develop treatments for specific syndromes

Sleep disorders are among one of the most common behavioral disturbances in persons with AD, with 25% to 50% having major sleep problems and almost 75% sleeping for extended periods during the day [44]. Sleep disturbances cause excessive caregiver burden and have a negative impact on cognition and social isolation on both the caregiver and person affected by dementia [45]. Measuring sleep disturbance can be difficult. Caregiver reports are often unreliable, and polysomnography measurements in a laboratory setting are not simple to perform. Ambulatory devices are becoming more widely available, although they may not give information about sleep stages [46]. Light therapy to entrain the biological clock has proven to be beneficial in randomized, controlled trials by improving nighttime sleep and reducing daytime sleep [47,48]. Melatonin has not been found to be useful [49]. Cognitive behavioral therapy for insomnia also reduces nighttime wakefulness [50].

Agitation/aggression is a common behavioral symptom of AD. It is clinically significant in approximately 20% of people with dementia in a community setting and in nearly 50% of people in care facilities [1]. The first line of treatment should always be to remove the source of the agitation whenever possible. Psychological and social treatments, like music, massage therapy, or caregiver education, might work, but medication may be necessary in more extreme cases. Although antipsychotics have modest benefits, they also have serious adverse effects, such as increased risk of cerebrovascular events and mortality. Carbamazepine demonstrated significant benefits in three small trials, but valproate has not proven useful. The antidepressant citalopram has been shown to be as effective as risperidone [51], an atypical antipsychotic, in the treatment of agitation. Several other antidepressants were not found to be useful for agitation [52]. Fewer people on memantine

develop agitation [53]. Because it is not clear whether the drug helps those who are already agitated or prevents people from becoming agitated, ongoing trials are awaited. Future studies should focus on psychosocial interventions for less severe agitation, short-term medication for the most severe cases, and combinations of the two, or sequential algorithms for most participants.

Diagnosing and treating depression in patients with AD is complicated. There is often considerable overlap with apathy and late-life depression unrelated to AD [54,55]. Latent class analysis, which is a model-based clustering approach that characterizes heterogeneity in symptom profiles at the patient level, may prove useful in diagnosing depression in AD patients [56,57]. A recent meta-analysis suggests that antidepressants do not have strong effects on late-life depression [58]. Similarly, the Depression in Alzheimer's Disease Study–2 trial did not find a positive effect of sertraline for depression in AD [59,60]. The efficacy of selective serotonin reuptake inhibitors for depression in Parkinson's disease has not been established either. However, treatments such as tricyclic antidepressants and a dopamine agonist (pramipexole) have shown some efficacy in treating depression in Parkinson's disease [61,62]. Looking forward, there are pathologies that could reveal potential targets for treating depression in AD. Neuropathology in monoamingergic networks may be related to depression [63], as may the number of corticotropin-releasing hormone neurons in the hypothalamus [64]. Biomarker analysis and associated genetic polymorphisms might also shed some light on the depression in AD. The finding that small hippocampal volume in late-life depression predicts subsequent dementia indicates that brain imaging may also be useful [65].

Psychoses are common in AD patients. Although some are mild and run their natural course without causing much stress, others, such as delusions, can be serious and a danger to both persons with the disease and caregivers [66–68]. Whether and when the physician should begin treatment depends on the frequency and severity of symptoms. The drugs currently used to treat psychoses in dementia, atypical antipsychotics, have limited efficacy (see earlier in the text) and should only be used as a last resort [52]. Treating any of these heterogeneous symptoms is likely to lead to only modest overall effect. A much better understanding of the pathophysiology of psychosis in dementia is needed.

Apathy is the most common and persistent NPS in AD patients [1,69]. It is defined as diminished motivation for at least 4 weeks, accompanied by any two of the following: reduced goal-directed behavior, reduced goal-directed cognitive activity, and reduced emotions [70]. Because these diagnostic criteria were newly formulated in 2009, assessment instruments are still being refined. Overlap between apathy and executive dysfunction has emerged in many studies [71–73], which may help to shed light on underlying causality because both are related to dysfunction of thalamic-prefrontal-subcortical circuitry. Donepezil has been shown to reduce apathy in people with moderate to severe AD [74]. Methylphenidate has shown efficacy in several small uncontrolled trials [75–79] and one controlled trial [80], and is being followed up in a larger trial of 60 participants. Various other drugs (including amantadine, d-amphetamine, and modafinil) have shown mixed results [81]. Selective serotonergic reuptake inhibitors may contribute to apathy. One challenge for the field is the relative paucity of trials targeting apathy in dementia. As with many NPS, imaging data may help pinpoint areas of the brain that are affected [82]. Apathy in AD is associated with gray matter atrophy in the anterior cingulate cortex and the left supplementary motor area [83,84]. People with AD and apathy also have more white matter hyperintensities [71,85] and a mixed pattern of reduced and elevated blood flow in different regions, thereby suggesting that the brain may be trying to compensate for the reduced blood flow. People with dementia and apathy also show a blunted response to d-amphetamine [86], suggesting problems with the brain reward system. Better appreciation of phenomenology,

neuroimaging, and pharmacology might help optimize treatment approaches for apathy in dementia.

Not infrequent NPS occurring in those with more severe dementia are disinhibited and aggressive behaviors that appear to result from loss of executive control of behavior, sometimes referred to as executive dysfunction syndrome [87]. When it occurs, executive dysfunction syndrome is another potential target for treatment, although specific diagnostic criteria for executive dysfunction syndrome in dementia are needed. Executive dysfunction syndrome often manifests in people who have suffered acute brain damage affecting frontal-subcortical loop functioning, but it also emerges in people with degenerative cognitive impairment [87,88]. It is characterized by executive cognitive deficits, emotional apathy, inattention, excessive and inappropriate jocularity, social inappropriateness, and impulsivity [89]. Relevant domains on the NPI-C include disinhibition, aberrant motor behavior, aberrant vocalizations, and aggression [10]. Disturbances in any of three specific "behavioral" neuronal circuits originating in frontal cortex might contribute to executive dysfunction syndrome. These circuits can be modulated by ascending neurotransmitter tracts, including dopaminergic, noradrenergic, acetylcholinergic, and serotonergic inputs, any of which might prove useful targets for treatment [87]. Dopamine augmentation, for example, relieved perseveration behavior in a small number of people with dementia [90], and amantadine has also been used in a small number of people for the same purpose [91]. Study of the pathophysiology and brain imaging should also shed light on the neuropathogenesis of executive dysfunction syndrome.

8. Funding and regulatory issues

The lack of consensus about how to define NPS in AD has been an obstacle to drug development. Historically, the construct "behavioral and psychological symptoms of dementia (BPSD)" was suggested as a target for drug development in people with dementia with NPS, but this was considered too broad a categorization by the U.S. Food and Drug Administration (FDA) [52]. Focusing on specific NPS syndromes in AD has been considered a better approach. From the March 2000 meeting of the FDA Psychopharmachological Drugs Advisory Committee, some consensus emerged on "Psychosis of Alzheimer's disease" as a distinct entity [6]. However, there was limited consensus on how to define agitation as a possible target.

Defining other syndromes of AD should be a focus of future work. DSM criteria are not needed for the FDA Division of Psychiatric Products to endorse a clinical entity for drug development. Rather, the entity must be sufficiently well characterized, such that it can be studied and described in labeling, and be attributable to AD. It should also be reasonably well accepted in the clinical/academic community and distinguishable from recognized clinical entities in other settings. PAD is the only target formally endorsed by the FDA [92].

The FDA would beam enable to carving out additional NPS targets by combining signs and symptoms into distinct entities for drug development. The challenge would be making the case that a particular cluster of symptoms is a well-defined and distinct entity. It would also have to have acceptance in the clinical/academic community. For example, to demonstrate that depression associated with MCI is distinct from other types of depression, it would have to be shown that the phenomenology, course, and response to treatment are different than for other types of depression.

The FDA has required a co-primary outcome measure in AD trials. A greater distinction regarding PAD has to be made. The agency is, however, willing to consider arguments against this stipulation, but with caution. Other aspects of study design would depend on the specific entity being targeted.

9. Conclusions and recommendations

Regarding assessment of NPS in AD, any new NPS tools would need to be developed with standard methodology and to be shown to have at least face validity. An acceptable key secondary measure would be one that targets a separate domain, for example, improved functional capacity, rather than simply replicating the primary symptom domain assessed by the primary measure.

NPS could qualify as a secondary outcome in a disease modification trial, but this assumes that a single drug targets both cognitive and behavioral symptoms, which may not be realistic. A better approach might be to use time to NPS emergence as an endpoint in trials targeting specific NPS.

Currently, there are very few medications that are useful for NPS in patients with AD. Antipsychotics are perhaps the most widely used for NPS, but their efficacy is modest at best, and the potential for serious side effects remains a concern. Key questions that are emerging include the following: Can the assessment of NPS be improved? Are neuropsychiatric conditions risk factors for dementia such that targeting them might reduce dementia risk? Do these syndromes or their successful treatment modify the course of dementia? What is the efficacy and safety of existing treatments? And can safer, more efficacious drugs be developed?

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