Geriatric Psychopharmacology: Evolution of a Discipline

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The development of geriatric psychopharmacology was built on advances in geriatric psychiatry nosology and clinical pharmacology and on increased investment in aging research by the National Institute of Mental Health and by academic institutions. Application of the US Food and Drug Administration's geriatric labeling rule provided further impetus. Developments in the knowledge about 3 principal classes of medications (antidepressants, antipsychotics, and treatments for Alzheimer's disease) illustrate the trajectory of geriatric psychopharmacology research. Nonetheless, the loss of information about age effects that has resulted from applying age exclusion criteria in studies limited to either younger adults or geriatric patients is regrettable. Antidepressant trials have moved from studying younger and medically well "geriatric" samples to focusing on "older old" persons and those with significant medical comorbidity including coronary artery disease, cerebrovascular disease, and dementia. Increased specificity is reflected in studies of relationships between specific neuropsychological deficits, specific brain abnormalities, and antidepressant responsiveness. Clinical trials in older adults have demonstrated that the efficacy of antipsychotic medications continues across the lifespan, but that sensitivity to specific side effects changes in older age, with poor tolerability frequently mitigating the benefits of treatment. Treatments for Alzheimer's disease have fallen within the purview of geriatric psychopharmacology. The research focus is increasingly shifting from treatments to slow the course of cognitive decline to studies of early diagnosis and of interventions designed to prevent the development of deficits in vulnerable individuals. The importance of geriatric psychopharmacology will grow further as the average lifespan increases all over the world.

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The history of geriatric psychopharmacology can be best understood in relationship to 4 parallel developments that occurred during the last quarter of the 20th century: (1) the development and publication of standardized criteria as a foundation for reliable psychiatric diagnosis during the 1970s[1–4]; (2) the identification, study, and subsequent US Food and Drug Administration (FDA) approval of medications to treat the indications of psychiatric syndromes and disorders[5]; (3) the development of an infrastructure and funding mechanisms within the National Institute of Mental Health (NIMH) to develop academically based investigator-scholars in geriatric mental health; and (4) the increasing awareness of the "graying of America,"[6] the call to address this "demographic imperative" by augmenting the knowledge base in geriatrics at academic centers,[7] and an increasing focus on geriatric mental illness.[8] Applied to the disciplines of pharmacology and therapeutics, these events led to the development of scientists and programs of study devoted to investigating disorders of later life and the efficacy and tolerability of medications in geriatric patients. It can be argued that focused geriatric studies might have had a paradoxical effect of limiting our ability to identify aging effects. Specifically, our ability to determine the contributions of factors related to chronological aging has been limited by the segregation of studies of older adults from those of younger samples. A broadening of age inclusion criteria in psychopharmacology studies supported by industry and the NIMH would be required to more precisely identify aging effects on efficacy and tolerability.

A decade passed before these NIMH investments bore fruit. Sufficient information was available in the 1980s to support the launch of peer-reviewed journals devoted to geriatric psychiatry, such as *International Journal of Geriatric Psychiatry* in 1985, *International Psychogeriatrics* in 1989, and the US-based *American Journal of Geriatric Psychiatry* in 1993. The development of a knowledge base also led to the publication of early textbooks of geriatric psychopharmacology,[9–12] including the first of 4 editions of a textbook devoted to clinical geriatric psychopharmacology.[13] The historical forces that contributed to our current knowledge can be best understood by reading the too-often overlooked introduction sections of geriatric psychiatry texts that review the evolution of the discipline.[14]

This article provides a historical overview of developments that contributed to advances in geriatric psychopharmacology followed by a description of the trajectories of research advances in 3 principal classes of medications: antidepressants, antipsychotics, and medications used to treat Alzheimer's disease. An exhaustive review of developments in all classes of medications or of each medication in the classes discussed is beyond the scope of this review. We focus on prototypical medication classes to describe the trajectory of research in geriatric psychopharmacology generally.

Changes in the FDA Drug Approval and Labeling Process

To obtain FDA approval for standard indications, industry trials typically focus recruitment on patients who would

be at the greatest likelihood of benefiting from a medication and are at lowest risk for suffering adverse events. Therefore, phase 3 studies did not typically include either geriatric patients or patients with significant medical comorbidity to minimize the risk for adverse outcomes. The "geriatric use" rule of 1997[15] required industry to provide supplemental data on specific classes of medications used to treat geriatric patients. "Psychotropic medications" were included among the classes covered by the geriatric use rule. The conceptualization of geriatric patients as a "special population" that required additional empirically derived labeling instructions for drug approval required industry to specifically study the effects of older age on a medication's pharmacologic properties. Nevertheless, application of the geriatric use rule does not require the inclusion of statistically meaningful numbers of older adults or patients with aging-related medical comorbidity in phase 3 studies. Meaningful data on geriatric use would require the inclusion of a broad and representative age range of subjects in single studies or meta-analyses that addressed age effects across mixed-aged adult and geriatric studies. Such data remain unavailable. Also, the requirement for geriatric labeling does not specifically address psychopharmacologic issues related to significant comorbidity that challenge geriatric psychiatrists.

Applications of Advances in Psychopharmacology to Geriatric Psychopharmacology

Although this review focuses on geriatric psychopharmacology, the discussions of specific medication classes have been informed increasingly by parallel developments in pharmacologic research. Geriatric psychopharmacology has benefited from discoveries ranging from the identification of neurotransmitters and their physiologic effects to developments in our understanding of pharmacodynamic effects and pharmacokinetic processes. For example, the development of an assay to assess the cumulative serum anticholinergic activity associated with medication use[16] was followed by the correlation of increased activity with anticholinergic side effects in geriatric patients.[17] Similarly, evidence that aging is associated with decreased dopamine functioning in corticostriatal pathways[18] explained the association between older age and the increased prevalence of both extrapyramidal symptoms and tardive dyskinesia that had been observed with treatment using conventional antipsychotic medications.[19,20] Despite aging-related decreases in renal and hepatic function, the "pharmacokinetic assumption" that aging would result in high concentrations of *most* psychotropic medications has not been supported empirically.[21] An aging-related slowing of demethylation required for the metabolism of medications such as diazepam and the tertiary amine tricyclic antidepressants (TCAs) stands as the major exception to the absence of clinically significant age effects on drug metabolism.[22] The dearth of pharmacokinetic studies that include a broad age range continues to limit our knowledge of both the pharmacodynamic and pharmacokinetic effects of aging and has contributed to the hope that population pharmacokinetics will clarify the effects of aging on medication effects.[23,24]

Definition of *Geriatric*

As noted above, the inclusion of physically healthy participants over the age of 60 in efficacy studies does not address either the efficacy or the tolerability of medications in patients with comorbid medical conditions that are commonly seen in older persons. Also, defining *geriatric* on the basis of chronological age fails to capture both the nonlinearity of changes in physiologic processes and the increased biologic heterogeneity that is associated with aging.[25,26] The standard "geriatric" cutoff age of 65 years or older is arbitrary and evolves out of regulatory definitions rather than empirical studies of the aging process. It is not surprising that the earliest geriatric studies included the "lowest-hanging fruit," ie, younger ambulatory patients. Thus, the seminal acute and maintenance antidepressant trials conducted in the 1980s by Georgotas and colleagues recruited medically well outpatients and applied an inclusion criterion of age 55 or older.[27–29] Early reviews[30] pointed to the need for randomized controlled trials (RCTs) of antidepressants in the older old to guide treatment of "truly" geriatric patients. As discussed in later sections, recent studies have focused on more "geriatric" questions; this has included requiring age 70 or above for inclusion and studying the efficacy of medications in patients with comorbid conditions.[30]

ANTIDEPRESSANTS

Efficacy for Major Depression

Early NIMH-supported RCTs demonstrated the efficacy of both nortriptyline and phenelzine for the acute and continuation treatment of geriatric depression.[27,28] Although a small-sample early report failed to demonstrate the efficacy of nortriptyline for maintenance therapy,[29] results from an extension of this trial were positive,[31] but never published because of the premature death of Dr Anastasios Georgotas, the lead investigator. Subsequently, a large-scale NIMH trial demonstrated the clear superiority of nortriptyline maintenance for recurrent geriatric depression among patients 60 and older.[32] By 1994, a sufficient number of controlled studies demonstrating efficacy and tolerability were available for the NIMH Consensus Development Conference to recommend secondary amine TCAs as the first-line treatment among TCAs for geriatric depression.[33]

The FDA approval of fluoxetine in 1987 was followed by approval of other medications in the selective serotonin reuptake inhibitor (SSRI) class. Eli Lilly received a specific indication for fluoxetine as a treatment for major geriatric depression in 1999 based on statistical separation from placebo in a large-sample trial.[34] Although approvals for the treatment of geriatric depression have not been obtained for other SSRIs, completion of acute and continuation/maintenance trials in older adults has become standard during the development of new antidepressants. A sufficient number

of trials have been completed for the publication of meta-analysis demonstrating that second-generation antidepressants are effective[35] and have an efficacy that is comparable to that of TCAs, although side effect profiles tend to favor SSRIs over the classical TCAs.[36,37] Poorer tolerability to TCAs among older adults results, in part, from aging-related increases in sensitivity to the anticholinergic and α_1-blocking properties of these medications. These changes in pharmacodynamic sensitivity are thought to mediate aging-related increased risks for orthostatic hypotension and falls associated with TCA treatment.[21]

Efficacy in the Older Old

The trial conducted by Roose and colleagues[38] in "old-old" patients addressed the dearth of efficacy in data in older geriatric patients by applying an inclusion criterion of age 75 and above. Although results on the primary outcome measures were negative, secondary analyses revealed that more severely depressed participants and those with early-onset depression were more likely to benefit from the antidepressant. These results point to the heterogeneity of geriatric depression and indicate that neuropsychological factors and underlying aging-related changes in brain structures may diminish the efficacy of antidepressants.[39,40] The finding by Reynolds et al[41] that comorbid anxiety and the severity of medical comorbidity moderated the efficacy of SSRI maintenance treatment in patients 70 and older added to knowledge about how aging-related factors moderate antidepressant efficacy.

Efficacy in Psychotic Depression

Early studies in the United Kingdom[42] and United States[43] reported that approximately 45% of older adults hospitalized for depression have associated delusions. Trials of antidepressants demonstrating that delusional depression was associated with a poor response to classical TCAs[44–46] were followed by the observation that older patients with delusional depression had a 2-fold greater 1-year mortality than patients with nondelusional major depression.[47] Although an early RCT demonstrated the efficacy of combining a TCA with a conventional antipsychotic in younger adults,[48] the first RCT of combination treatment in geriatric patients with psychotic major depression was negative.[49] A recent RCT of delusional depression using high doses of the better-tolerated SSRI class of antidepressants in combination with an atypical antipsychotic demonstrated comparable efficacy in young adults and older participants, who comprised more than 50% of the sample.[50]

Depression Associated With Comorbidity

Conceptualization of comorbidity rather than chronological age as central to the definition of *geriatric* stimulated RCTs conducted in depressed patients with comorbid conditions. Early approaches to depression with medical comorbidity used stimulants, such as methylphenidate, to improve nonspecific symptoms, including anergy, lack of motivation, and fatigue. Despite open trials suggesting that psychostimulants may improve symptoms associated with debilitation[51] and "negative symptoms" in patients with dementia,[52] RCTs have not demonstrated efficacy among patients who meet criteria for major depression.[53]

Most antidepressant trials in patients with Alzheimer's disease and major depression have been negative,[54] which has been attributed to high placebo response rates, instability of depressive symptoms in dementia patients, and insensitivity of symptoms caused by dementia to antidepressant effects.[55] Provisional diagnostic criteria have been proposed to better capture the major depression that occurs in association with Alzheimer's disease.[56,57] Nevertheless, the validity of these criteria must be established and reliable scales for assessing depression in these patients must be developed before the sensitivity of depression in dementia to antidepressants can be meaningfully assessed.

The past decade has seen an increasing focus on investigating whether specific types and locations of central nervous abnormalities moderate responsiveness to antidepressants. Studies of specific neuropsychological deficits and associated underlying neuropathology have been promising. The construct of "vascular depression" was developed to describe major depression associated with particular clinical characteristics, including apathy, excess disability, and impairment in executive functioning.[58] A similar clinical syndrome was contemporaneously described among older patients with major depression associated with diffuse white matter hyperintensities attributed to small vessel cerebrovascular disease.[59] Studies of geriatric depression associated with executive functioning have demonstrated that patients with impaired executive function performances have both diminished antidepressant response[60,61] and pathology in white matter tracts in corticostriatal pathways.[62,63] Further analysis of the data from the study of the "old-old"[38] complemented these findings by demonstrating that the size of drug-placebo differences had been diminished in the RCT because of negative interaction between the SSRI and the presence of executive impairment among participants.[64] Parallel findings were reported from an RCT of magnetic resonance imaging–defined vascular major depression, which demonstrated that the presence of white matter hyperintensities and executive impairment independently predicted a diminished antidepressant response to the SSRI.[65] Thus, the trajectory of geriatric antidepressant trials has moved from examining the nonspecific construct of chronological age to demonstrating the moderating effect of specific neurobiological factors on response to antidepressants.

Studies of the relationships between both recent cerebrovascular accidents[66] and coronary artery disease (CAD)[67] with depression have demonstrated a higher prevalence of major depression in patients with these vascular disorders and poorer outcomes if depression is present. Antidepressant trials in patients with poststroke depression have demonstrated efficacy for acute treatment with the secondary amine TCA nortriptyline,[68,69] prophylactic efficacy of both

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nortriptyline and escitalopram,[70] and decreases in long-term mortality from vascular disease in patients who underwent a short-term course of poststroke antidepressant treatment, whether or not depression had been present initially.[71] Trials conducted in patients with major depression and CAD have demonstrated the efficacy of antidepressants,[71,72] particularly in patients with more severe and recurrent forms of depression.[4] Inclusion in these trials was based on the concurrent medical condition rather than chronological age, an approach consistent with emphasizing aging-related medical conditions rather than chronological age as moderators of treatment response.

ANTIPSYCHOTICS

Although antipsychotic medications are effective for treating bipolar mania and, in some instances, bipolar depression, RCTs in geriatric patients have been limited to patients with schizophrenia and the psychiatric complications of dementia.

Schizophrenia

Early double-blind studies demonstrated the efficacy of conventional antipsychotic medications in older patients with schizophrenia.[73–75] However, texts written as early as the 1970s[76–78] warned that α_1-, cholinergic- and histaminic-blocking properties of low-potency medications and the stronger dopamine-blocking properties of high-potency conventional antipsychotics made older patients particularly vulnerable to the development of clinically significant side effects. Subsequent research demonstrated that both a "late-onset" subtype of schizophrenia, which is marked by positive symptoms, and the positive symptoms of early-onset patients who have aged are responsive to conventional antipsychotic drugs,[79,80] although lower doses are needed to treat positive symptoms in older patients than in younger adults.[81] Studies of relationships between age and both the frequencies and types of extrapyramidal symptoms (EPS) associated with conventional antipsychotic treatment demonstrated that older patients are more likely than younger patients to experience dystonic reactions, but that antipsychotic-induced parkinsonism, including tremor and rigidity, is common in older patients.[82] The increased incidence, prevalence, severity, and persistence of tardive dyskinesia (TD) in older patients treated with conventional antipsychotic medications[19,83–85] have been a major factor limiting the use of these medications in geriatric psychiatry. Although investigators have pointed out the difficulty of distinguishing between risks for TD conferred by chronological age and those due to prolonged exposure, presumed aging-related brain changes[81,82] and the frequency and severity of TD in older patients supported the replacement of conventional antipsychotics with atypical antipsychotic medications for treating older patients with schizophrenia.

The FDA approval of clozapine in 1989 provided the first atypical antipsychotic medication and a treatment associated with a lower risk for EPS and TD. However, clozapine can be particularly problematic for older patients due to increased vulnerability of older patients to antimuscarinic, hypotensive, and sedative side effects and to the development of agranulocytosis during clozapine treatment.[86] Therefore, clozapine has been used primarily to treat psychotic disorders in patients who have EPS-predisposing comorbid conditions, such as Parkinson's disease and Lewy body disease, both of which increase their sensitivity to developing EPS in response to antipsychotic treatment. The small number of RCTs conducted with atypical antipsychotic medications in older patients with schizophrenia indicate that target doses of these medications are generally well tolerated and effective.[87,88] Also, seniors treated with atypical antipsychotics have demonstrated greater adherence and lower risk of TD than those who receive conventional agents.[89,90]

Older age is known to be associated with an increased prevalence of both obesity and type II diabetes, diminished glucose tolerance, and hyperlipidemia even in the absence of antipsychotic medication treatment. Nonetheless, concerns about metabolic side effects of atypical antipsychotic medications may limit their use in older patients.[91,92] The exclusion of a comparison group of older patients from most controlled studies of schizophrenia, including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE),[93] has precluded systematic analysis of how older age affects the incidence or severity of metabolic abnormalities during atypical antipsychotic treatment. However, a 12-week trial of olanzapine in psychotic depression demonstrated that young adults and participants 60 years and older had statistically significant and comparable elevations in triglycerides and cholesterols over a 12-week period.[50] While available data support the use of atypical antipsychotic medications in older patients with schizophrenia, sound practice dictates regular monitoring of metabolic parameters and interventions to address metabolic abnormalities that develop.

Antipsychotic Treatment of the Psychiatric Complications of Dementia

Agitation and psychotic symptoms are common in Alzheimer's disease, with prevalence estimates ranging between 30% and 70%.[94–96] The demonstration of untoward consequences of these psychiatric complications, including earlier institutionalization[97] and increased caregiver burden,[98] supported assessing the efficacy of interventions to reduce psychiatric comorbidity. Conventional antipsychotics were prescribed to treat these complications, but meta-analysis and systematic reviews demonstrated only modest benefits.[99,100] A small RCT with haloperidol demonstrated the importance of appropriate dosing and careful monitoring to keep patients within the narrow therapeutic window associated with clinical improvement without problematic EPS.[101] Epidemiologic evidence of a relationship between psychotropic medications and incidence of hip fractures among nursing home residents[102] changed the treatment of psychiatric complications of dementia and increased the role

of geriatric psychiatrists in long-term care. Demonstration of a dose-dependent hip fracture risk and the subsequent finding that the intensity of pharmacotherapy administered to nursing home residents was predicted by the size of the primary care physicians' practices rather than by identifiable patient characteristics[103] led to federal legislation to regulate prescribing of psychopharmacologic agents in facilities that treat Medicare recipients. State inspection agencies welcomed the involvement of geriatric psychiatrists as nursing home consultants to monitor psychotropic prescribing to assure that residents were not treated with legislatively defined "unnecessary medications" or doses.

The introduction of atypical antipsychotic medications in the 1990s was associated with industry's conducting RCTs to test the efficacy of second-generation compounds that would avoid the problems of sedation and orthostatic hypotension associated with low-potency conventional agents and the EPS associated with high-potency agents. Positive placebo-controlled RCTs with both risperidone[104] and olanzapine[105] were reported, with both dose-finding placebo-controlled studies again demonstrating the presence of a narrow therapeutic dosing window for older patients with dementia. The CATIE Alzheimer's trial[106] compared the effectiveness of 3 atypical antipsychotic medications to placebo for psychiatric complications of dementia using time to discontinuation due to either lack of efficacy or poor tolerability as the primary outcome measure. Although the times to discontinuation due to lack of efficacy were longer among participants randomized to both olanzapine and risperidone than in subjects who received placebo, this greater efficacy was "offset" by the higher discontinuation rate among subjects who received active medication.[106] CATIE Alzheimer's trial results highlight the importance of monitoring patients to determine relative benefits versus risks of antipsychotic treatment and of considering nonpharmacologic interventions to manage psychiatric symptoms associated with dementia. A subsequent analysis of pooled data across many atypical antipsychotic RCTs demonstrating a greater mortality rate among patients who had received active medication than those who had been randomized to placebo[107] led to an FDA black box warning and the end of industry-supported trials of atypical antipsychotic medications in dementia patients. In view of these safety concerns, an APA consensus statement on the treatment of Alzheimer's disease[108] and an American College of Neuropsychopharmacology White Paper[109] were published to evaluate the risk:benefit ratio for using atypical antipsychotics to treat psychiatric complications of dementia.

Research into treating the behavioral complications of dementia has been further limited by the absence of standard criteria for defining constructs such as agitation and of tools to assess severity. The FDA pointed out that "agitation" cannot be considered an approvable indication until consensus diagnostic criteria and reliable assessment tools are developed.[110] In contrast, the publication of criteria for the psychosis of Alzheimer's disease[111] led to FDA approval of this indication, although the greater mortality risk with atypical medications is an obstacle to the use of those drugs for this syndrome.

ALZHEIMER'S DISEASE TREATMENTS

Studies of Alzheimer's disease treatments have increasingly fallen within the purview of geriatric psychopharmacology. Early treatments were both nonspecific and largely ineffective. Dihydroergotoxine, a vasodilator with mild monamine oxidase inhibitor properties, was approved for treatment of "senile mental decline" in the 1970s, which was consistent with the then-prevalent assumption that underlying vascular disease played a pathogenic role in late life–onset dementias; however, benefits of dihydroergotoxine were minimal, and trial results are difficult to interpret because standardized diagnostic criteria and reliable assessment tools were not available.[112]

Laboratory studies of brains of patients with Alzheimer's disease in the late 1970s demonstrated that concentrations of brain acetylcholine (ACh) were correlated with both the severity of cognitive impairment and the numbers of senile plaques in dementia patients.[113] These findings were followed by the demonstration of degenerated cholinergic pathways in Alzheimer's disease,[114,115] leading up to the hypothesis that deficiency in ACh was central to the cognitive impairment of Alzheimer's disease.[116] Initial attempts to supply damaged neurons with choline, a precursor of the neurotransmitter ACh, were both impractical and ineffective. Subsequent studies that attempted to slow the metabolism of available ACh led to the development of the cholinesterase inhibitor class of antidementia medications. RCTs using cholinesterase inhibitors in systematically diagnosed patients with mild to moderate dementia have been largely positive in terms of slowing the rate of cognitive decline over a period of up to 2 years,[117,118] with some variability in evidence supporting one or another medication in this class for patients at specific stages of disease or with other types of dementia. Although donepezil has received approval for moderate to severe as well as mild dementia, an absence of head-to-head studies demonstrating the clear superiority of one agent over another is consistent with considering the 4 approved cholinesterase inhibitors as comparably effective overall. The use of tacrine, the first cholinesterase inhibitor approved to treat Alzheimer's disease, has been limited because of a high risk for hepatotoxicity that is not associated with alternative agents. Paradoxically, demonstration of the efficacy of cholinesterase inhibitors in 6-month studies has discouraged the conduct of longer term placebo-controlled trials on ethical grounds. While data from the available open-label add-on trials suggest possible benefits from continued treatment with anti-Alzheimer's medications in some patients,[119] no definitive recommendations for continued treatment can be made without large-scale RCTs of longer duration.

Memantine, a partial antagonist of the *N*-methyl-D-aspartate glycine receptor, has been studied for Alzheimer's disease based on the underlying theory that the excitatory

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properties of glycine contribute to the death of damaged Alzheimer's disease neurons. The 2 pivotal memantine trials for moderate to severe Alzheimer's disease conducted in the United States were led by geriatric psychiatrists,[119,120] demonstrating the extension of geriatric psychopharmacology studies into disorders involving structural brain disease.

Alzheimer's disease investigators have recognized that the effective treatment must occur early, before neurons are irreversibly damaged by the deposition of abnormal amyloid and tau protein. The demonstration that radioligand imaging identifies abnormal brain amyloid deposits in patients with mild Alzheimer's disease[121,122] and recent evidence that abnormalities in concentrations of cerebrospinal fluid amyloid and phosphorylated tau predict the development of Alzheimer's disease provide an early-detection foundation for future interventions.[123] Early interventions with novel pharmacologic strategies, including immunization and amyloid-modifying medications that are under development, have the potential for postponing the onset or reducing the risk of Alzheimer's disease in vulnerable individuals.

Putative Cognitive Enhancers for the Psychiatric Complications of Alzheimer's Disease

RCTs designed to study whether specific medications decrease the rate of cognitive decline in Alzheimer's disease patients have led to secondary analyses of whether improvement in psychiatric symptoms is greater in participants who received active medication compared to those allocated to placebo. Analyses for improvement in psychopathology in association with cholinesterase inhibitors[124–126] and memantine[127] have generated mixed results, and hypothesis-driven RCTs that demonstrate the efficacy of putative cognitive enhancers for specific psychiatric phenomena remain unavailable.

GERIATRIC PSYCHOPHARMACOLOGY: THE FUTURE

The impact on psychiatric disorders of physiologic changes associated with normal aging and of aging-related diseases is consistent with considering geriatric psychiatry as being probably the most "medical" of the psychiatric subspecialties. The central role of medical issues in treating older psychiatric patients was used to support classifying geriatric psychiatry within the purview of liaison psychiatry a quarter century ago.[128] Furthermore, geriatric psychiatry is also at the boundary between psychiatry and neurology. The contributions of structural brain changes associated with aging and of aging-related brain disease to the so-called functional psychiatric conditions support considering geriatric psychiatry as a model for integrating psychiatry, neurology, and neuroscience[129] in a combined discipline of "neuropsychiatry."[130] For these reasons, geriatric psychopharmacology is the discipline that is best suited to study relationships between both general medical and neurologic conditions that are associated with aging and classical psychiatric disorders. Research in geriatric psychopharmacology has increasingly demonstrated that both physical and psychosocial factors influence the phenomenology and treatment response of psychiatric disorders in later life. The trajectory of research in this arena has been increasingly specific. The accumulation of new data about how specific medical and neurologic lesions contribute to psychiatric symptoms allows geriatric psychopharmacology to ask more precise questions about moderators of outcome. From this perspective, geriatric psychopharmacology has evolved into the prototypical psychiatric discipline for addressing questions at the boundaries between structure and function and between pathologic processes and psychiatric treatment. With the rapidly changing demographics, in view of the lengthening lifespan all over the world, the importance of geriatric psychopharmacology is expected to grow progressively over the next quarter century.

Drug names: clozapine (Clozaril, FazaClo, and others), diazepam (Valium and others), donepezil (Aricept and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), memantine (Namenda), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), phenelzine (Nardil), risperidone (Risperdal and others), tacrine (Cognex).

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