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Epigenetic Alterations Impact on Antipsychotic Treatment in Elderly Patients

Bryan M. McClarty¹, Daniel W. Fisher², and Hongxin Dong¹

¹Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, Chicago, IL 60611, USA

²Department of Neurology, Northwestern University Feinberg School of Medicine, 303 East Chicago Avenue, Chicago, IL 60611, USA

Abstract

Purpose of the review—Antipsychotics are commonly prescribed for the treatment of psychosis as well as behavioral and psychological symptoms of dementia (BPSD) in elderly patients. However, elderly patients often experience decreased antipsychotic efficacy and increased side effects, though the mechanisms underlying these changes with age are not clear.

Recent findings—Although aging can affect drug metabolism and clearance through changes in renal and hepatic function, additional pharmacokinetic and pharmacodynamic changes due to aging-induced epigenetic alterations also impact processes important for antipsychotic function. Epigenetic mechanisms account for some of the altered efficacy and increased side effects seen in elderly patients.

Summary—Both clinical and animal studies from our group and others have demonstrated a plausible epigenetic mechanism involving histone modifications that can adversely affect the efficacy of antipsychotics and increase their side effects in elderly patients. Hopefully, further investigation of this mechanism will benefit elderly patients who need treatment for psychosis and BPSD.

Keywords

Epigenetics; Histone modification; Antipsychotics; Aging; Drug efficacy; Side effects

Introduction

Many elderly individuals suffer from neuropsychiatric disorders that necessitate treatment with antipsychotics, and the number of patients needing treatment will increase substantially as the population ages [1]. However, the benefits of available antipsychotics are offset by

Corresponding author: Hongxin Dong, MD. PhD., Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 303 E. Chicago Ave, Ward 7-103, Chicago, IL 60611, 312-503-3433 (Office); 312-503-0466 (Fax), h-dong@northwestern.edu.

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neurological side effects, which are exaggerated in the elderly [2–4], even when using reduced dosages that are 1/3 of the regular adult dose [5–7]. As antipsychotics still constitute the primary class of medications used for the treatment of psychosis and behavioral and psychological symptoms of dementia (BPSD) [5, 8], it is urgent that we identify novel therapeutic approaches that can minimize the adverse effects of antipsychotics in aged populations.

Many factors may reduce the metabolism of antipsychotics and increase drug levels in the elderly, especially age- or disease-related deficits in renal and hepatic function [9]. Yet, age-related increases in antipsychotic side effects are not entirely explained by declining drug clearance, and it is well-known that aging causes widespread changes in metabolism and gene transcription [8, 10] that could affect drug action. In line with this, increasing reports suggest that the epigenetic landscape is greatly altered with aging [11, 12], and epigenetic alterations have been specifically shown to alter antipsychotic effectiveness in elderly patients [12, 13].

In this review, we briefly describe specific concerns associated with antipsychotic use in elderly patients. Then, we detail some of the most significant advances in understanding how epigenetic changes can influence antipsychotic action in the elderly by affecting pharmacokinetics through altered transcriptional control of important metabolic enzymes and transporters as well as pharmacodynamic changes at the target receptor level, leading to increased sensitivity of the elderly to antipsychotics.

1. Specific Concerns for Antipsychotic Treatment in Elderly Patients

Although antipsychotics may induce side-effects for all patients, these adverse effects in elderly patients are often more severe. Unlike younger patients, in whom antipsychotics are commonly used for on-label indications including schizophrenia or bipolar disorder, there is a higher rate of off-label prescriptions in older patients [14, 15]. Prescribing trends for antipsychotics in the U.S. were explored in 2008 and the investigators found that while 46% of patients between 18–65yo received different atypical antipsychotics for on-label indications, only 25% of elderly patients (>65yo) received antipsychotics for FDA-approved indications [16]. More recently, a German study noted that antipsychotic prescriptions for elderly patients with schizophrenia were rare, while patients with dementia represented a much larger proportion of patients on antipsychotics [17]. Due to the increase in off-label antipsychotic use in the elderly, a greater emphasis on elderly patients with dementia is reflected in the literature compared to elderly patients with schizophrenia.

For patients with dementia, antipsychotics are commonly used to treat the heterogeneous syndrome of depression, agitation, aggression, and psychosis known as BPSD. With Alzheimer's disease being the most common form of dementia, it is staggering to note that more than 80% of people with Alzheimer's disease develop BPSD during the course of the illness [18]. While antipsychotics are not FDA-approved for BPSD treatment, no other medication has resulted in better control of BPSD symptoms, especially psychosis, agitation, and aggression [19].

In elderly patients, physicians need to account for numerous special considerations that are less prevalent in younger patients. Reflecting this situation, an FDA black box warning was issued for atypical antipsychotic use in the elderly, especially patients with dementia, citing a 60 to 70% higher risk of all-cause mortality, mostly associated with higher rates of adverse cerebrovascular events and infections [19–21]. In addition, elderly patients have a higher rate of polypharmacy and polymorbidity, making drug interactions more likely and impaired metabolism and excretion due to renal and hepatic disease a greater concern [4, 22]

While the metabolic and cardiovascular complications of antipsychotic use in elderly patients are of obvious concern, there is a particularly disturbing increase in motor and cognitive side-effects in elderly patients compared to younger patients. In particular, elderly patients are much more vulnerable to parkinsonisms and tardive dyskinesia [23], which occur in more than 50% of aged patients [24–26]. The incidence of tardive dyskinesia following the use of typical antipsychotics is about 5 times higher in elderly patients compared to younger patients, and while atypical antipsychotics result in lower rates of motor side effects overall, elderly patients are still more prone to develop parkinsonisms and tardive dyskinesia after using these drugs as well [27–30]. Although an indirect measure of motor dysfunction and co-morbid with antipsychotic-induced autonomic dysfunction, elderly patients on antipsychotics are more likely to suffer falls [3].

Although the increased risk of motor side-effects with antipsychotics in elderly patients is clear, the presence of more severe cognitive side effects are more nuanced, due to high co-morbidities. While atypical antipsychotics have fewer cognitive side-effects than typical antipsychotics in young patients with schizophrenia, these same drugs have been suggested to accelerate cognitive decline in patients with dementia [31, 32]. However, the significance of these findings in terms of aging itself are hard to determine, as the confounding processes of dementia, co-morbidity with other diseases, and polypharmacy can obscure a more direct relationship between antipsychotic use and cognitive decline in elderly patients. Regardless, higher rates of depression, anxiety, and cognitive impairments have been reported for elderly patients on antipsychotics versus age- and health-matched control patients that are not exposed to antipsychotics [33].

In total, while the risk of increased mortality is clearly of great concern for antipsychotic use in elderly patients, increasing data suggests that motor and cognitive side-effects occur more commonly in this population as well. Accordingly, both pharmacokinetic and pharmacodynamic mechanisms for these side-effects have been suggested, and aging-related epigenetic alterations may underlie these changes.

2. Epigenetic Alterations in the Brain with Aging

Certain epigenetic changes, such as DNA methylation, are specific to the aging process and can be used to predict a human's age from a tissue sample simply through determining the methylation status of specific CpG sites [11]. Still, tissue-by-tissue and gene-by-gene differences are observed in aging-related epigenetic processes [34]. Overarching motifs for the aging brain exist, including hypomethylation at enhancers and hypermethylation at age-associated differentially methylated regions, decreased histone acetylation, increased/

decreased histone methylation, increased expression of certain miRNAs, and decreased sirtuin expression [12]. These epigenetic changes facilitate chromatin remodeling of certain genes during aging [35], and result in altered gene expression patterns that compromise cellular function and adaptations to environmental stimuli [36] as well as learning and memory [37, 38]. As some of the side-effects associated with antipsychotic use may dovetail with aging-related declines in cognitive ability, a review of some of the most salient epigenetic findings in terms of brain aging and cognition is helpful.

One of the most important changes with aging is the reduction of permissive histone markers and an increase in repressive markers, which can lead to subsequent deficits in neural plasticity [39–41]. For instance, age-related histone methylation in the hippocampus results in decreased *Arc* gene transcription, which leads to decreased plasticity and disruptions in memory storage and retrieval processes [42]. Decreases in H4K12ac at genes associated with learning may contribute to memory consolidation deficits in the aged hippocampus as well [43]. Further, increased levels of the repressive marker H3K9me3 are found in the aged mouse hippocampus and are associated with poorer memory function with corresponding hippocampal pathology, including reduced spine densities and synapse number [44]. Interestingly, when a histone methyl transferase was overexpressed therapeutically in aged hippocampi, H3K9me3 signatures were reversed and hippocampus-dependent fear memory was enhanced. In addition, reversal of histone methylation led to rescue of synaptic spine density, restoration of mushroom-spine shape, and increases in GluR1 and BDNF signaling [45]. Together, these findings suggest that aging can impact cognitive function through histone modifications [46], and that these alterations may also impede the efficacy of antipsychotics.

Interactions between environmental stimuli and aging may be especially important in shaping the epigenetic landscape. As an example, older rats with environmental enrichment had reduced levels of histone marker H3K4me3 in the CA3b region of the hippocampus while H3K9ac and H3K14ac levels were increased in the CA1 region compared to non-enriched older rats [47, 48]. Although these are just a few examples of the many studies looking at epigenetics, aging, and cognition, it has become clear that the process of epigenetic alterations due to aging and environmental stimuli lead to some of the aging-associated changes in cognition noted in the literature. Moreover, growing evidence from our group and others suggest that aging-and environmental stimuli-induced epigenetic alterations impact pharmacokinetic and pharmacodynamic processes influencing antipsychotic action [12, 13, 49, 50]. The following sections will discuss these effects in more detail.

3. Epigenetic Mechanisms of Pharmacokinetic Changes with Aging

In terms of the absorption, distribution, metabolism and excretion of neuropsychiatric drugs, both peripheral and central mechanisms must be considered due to the presence of the blood-brain-barrier (BBB) and other processes that affect central distribution and clearance [28, 51]. Though an increase in plasma antipsychotic concentrations between young and elderly patients has not been consistently shown and is likely to be generally negligible in otherwise healthy patients [28, 29], an increase in the brain/plasma ratio of antipsychotic

concentrations has been reported [28]. Mechanisms for this difference include breakdown of the blood-brain-barrier [52, 53] and decreased P-glycoprotein activity with age [54–56]. In part, this may help to explain why lower doses of antipsychotic are often needed in the elderly to avoid increased side-effect severity. The exact mechanisms driving this increase in distribution and decrease in clearance are still unclear.

While the influence of epigenetic interactions on absorption, distribution, metabolism and excretion are still incompletely characterized, significant research has suggested that there is a degree of epigenetic mechanism controlling over the metabolism and transport of psychoactive drugs [12, 13]. Epigenetic alterations have been shown to influence the transcription of multiple cytochrome p450 (CYPs), ATPases binding cassette (ABC) transporters, P-glycoproteins, and solute transporters, including the norepinephrine, dopamine, and serotonin transporters, SLC6A2, SLC6A3, and SLC6A4, respectively [12]. Consistent with these findings, reduced monoaminergic signaling in the elderly has been reported [46, 57]. As these enzymes and transporters have an important influence on antipsychotic and neurotransmitter concentrations at the neural membrane, it is very likely that these aging-related epigenetic changes can influence central pharmacokinetics.

Epigenetic processes that influence increased BBB permeability with aging are virtually unknown, though one study has shown that increased BBB permeability directly affects haloperidol concentrations in rats [52]. In addition, while P-glycoprotein activity decreases with aging [54–56], a direct link between epigenetic regulation, central antipsychotic concentrations, and this reduced activity has yet to be described. Future research into the interaction between aging, pharmacokinetics, and antipsychotics would be of great value for clinicians, pharmacists, and researchers who are working to develop more tolerable and effective treatment regimens for elderly patients.

4. Epigenetic Mechanisms of Pharmacodynamic Changes with Aging

While pharmacokinetic changes that occur with aging can increase the effective concentrations of antipsychotics at their target sites, pharmacodynamic alterations can impact the relative abundancy of target receptors, namely specific monoaminergic receptors, in elderly patients. Recent studies have focused on the dopamine 2 receptor (D2R) for typical and the serotonin 2A receptor (5-HT_{2A}) for atypical antipsychotics.

It has been shown that adjunct histone deacetylases (HDAC) inhibitor (HDACi) treatment has a positive effect on antipsychotic action and that the histone modifying function of HDAC2 is responsible for this effect [58, 49, 50]. One of the most complete characterizations of this effect was reported in a study showing that *5-Htr2a* transcription was de-repressed in mice treated with an atypical antipsychotic and the HDACi vorinostat (SAHA) through an HDAC2-dependent mechanism. Further, a bidirectional relationship between HDAC2 activity in the pre-frontal cortex and antipsychotic efficacy was observed in mouse models of schizophrenia, suggesting a pharmacodynamic mechanism in which adjunct HDACis improve antipsychotic function through increasing the available receptors targeted by antipsychotics [58]. Although this study showed a clear role for pharmacoeugenetics in antipsychotic action, it did not determine if aging also affects

HDAC2 activity. However, another post-mortem study demonstrated a correlation between H3K9K14ac markers at genes known to be decreased in schizophrenia, such as *Gad1*, *5-Htr2a*, *Tomm70a*, and *Ppm1e*, as well as a pattern of hypoacetylation at these promoters with age in neural tissue [59]. As HDACs reverse epigenetic repressing target receptor availability, and hypoacetylation was shown to occur at schizophrenia related gene promoters with aging, it was hypothesized that aging directly affects the availability of receptors targeted by antipsychotics and that adjunct HDACs reverse these changes through de-repression of transcription in elderly patients.

This hypothesis has been largely supported through post-mortem and radio-PET binding studies in elderly patients. Decreases in the density of receptors targeted by antipsychotics have been associated with aging-related increases in extrapyramidal and cognitive side effects [60, 61]. For instance, several investigators have observed decreased overall expression of D2R in the basal ganglia of elderly patients compared to controls [62–65]. Additionally, decreases in D2R and 5-HT2AR binding capacities are reduced with age in human and animal PET studies [66–69] as well as in post-mortem tissue studies comparing older to younger brains [70].

Because a disease process may also alter receptor expression in antipsychotic-treated patients, comparisons of schizophrenia or dementia patients with a healthy age-matched control is of value. In line with others studies on aging, postmortem and imaging studies have revealed early and prominent reductions in D2R and 5-HT2AR expression/density in the brains of patients with AD [71–73], though it remains unclear if this is due to aging or the disease process itself. Interestingly, for schizophrenia patients, D2R binding is unchanged in elderly patients with schizophrenia compared to age-matched healthy controls [74]. These studies in schizophrenia patients and healthy elderly patients suggest that the decreased efficacy seen with antipsychotics is not a factor of a disease process but instead a consequence of aging. Therefore, similar aging-related processes could undermine successful antipsychotic treatment in elderly patients with different disorders, though direct testing of this hypothesis is needed.

The information available on the epigenetic changes influencing antipsychotic pharmacodynamics is limited, and even less is known directly about how epigenetic changes that occur due to aging contribute. However, our recent research has built on the previously mentioned work, as we investigated links between age-related histone modifications, changes in receptor expression and functionality, and behavior in aged animals treated with antipsychotics. Our studies have focused on two important aspects of overall antipsychotic success, efficacy and side effect severity, and we have uncovered epigenetic contributions to both of these measures in mouse models.

Relevant to drug efficacy, we have demonstrated that histone modifications alter the expression of *c-fos*, an intermediate-early gene that estimates neural activity during a defined period, and influence the therapeutic actions of haloperidol, a typical antipsychotic drug, in aged mice [49]. With haloperidol treatment in aged but not young mice, C-Fos expression is associated with histone hypoacetylation of H3K27 and H4K12 at the *c-fos* promoter in the prefrontal cortex and nucleus accumbens [49]. These changes were

correlated with decreases in the ability of haloperidol to suppress avoidance responses during the conditioned avoidance response test. Finally, we found that co-treatment of haloperidol with two of the most common HDACis used in clinical studies [75, 76], either VPA or MS-275, restores both C-Fos expression in the cortex and nucleus accumbens as well as the ability of haloperidol to suppress the conditioned avoidance response in aged mice [49].

In addition to aging related epigenetic alterations reducing the utility of antipsychotics in aged patients, we further demonstrated that histone modifications at the *Drd2* promoter greatly influence EPS in antipsychotic -treated, aged mice. During aging, the *Drd2* promoter in striatal cells accrues increasing repressive histone markers, such as histone hypoacetylation at H3K9, H3K27, and H4K12, which can be reversed with adjunct HDACis. Interestingly, younger mice treated with these HDACis do not show the same degree of change in repressive histone marks, and the subsequent change in *Drd2* transcription is significantly less than in their aged counterparts. Aged mice treated with haloperidol show greater cataleptic behaviors than dose-matched younger mice [77]. Similar to the reversal of repressive histone modifications at *Drd2*, adjunct treatment of elderly mice with HDACis decreased cataleptic behavior to a significant degree, while younger mice showed similarly low degrees of catelptic behavior with or without adjunct treatment. Importantly, the dose of haloperidol used for these biochemical and behavioral studies was determined to result in similar blood, CSF, and brain tissue concentrations in young and aged mice, suggesting that pharmacokinetic alterations were not responsible for the observed differences in these assays.

In summary, our work supports an interaction between epigenetics, aging, and antipsychotics that partially explains why such drugs may show lower efficacy and greater side-effects in elderly patients. Further, we suggest a novel therapeutic approach for these patients that depends on using such drugs together with HDACis. Unfortunately, this work remains far from direct translation to the clinic, and future studies are needed to 1) identify other epigenetic factors, such as histone acetyltransferase activity, that may regulate the genes of receptors targeted by antipsychotics, 2) discover other affected genes using genome-wide, epigenetic analyses in aged mice following treatment with antipsychotics and HDACis, 3) investigate additional HDACis and atypical antipsychotics to broaden our findings, and 4) identify the most promising combinations for patients.

5. Conclusions

As antipsychotics remain among the most highly prescribed drugs in elderly patients, the reported increase in adverse side effects and decreased efficacy remains a significant issue. In addition, as unique concerns for disease and drug-drug interactions are associated with elderly patients, these complications make physicians wary when prescribing these medications. Although current guidelines and expert opinions rightfully urge physicians to keep the dose of antipsychotics low, it is clear that new strategies are needed, as the indications to treat the elderly with antipsychotics continues to expand.

Aging-related changes in the epigenetic landscape likely alter antipsychotic efficacy in elderly patients through pharmacokinetic and pharmacodynamic mechanisms. Epigenetic alterations influence the expression of specific metabolic enzymes and transporters, which are likely to lead to increased CNS distribution and decreased clearance of antipsychotics in elderly patients. From a pharmacodynamic perspective, epigenetic alterations can affect the expression, availability, and overall function of common monoaminergic receptors that are targeted by antipsychotics. While many different epigenetic mechanisms are likely to affect antipsychotic action, decreased permissive and increased repressive histone markers at important gene promoters are known to be at least partially responsible for the increased side effects and decreased efficacy of such drugs. As many of these changes are related to histone acetylation, it is particularly revealing that HDACis reverse repressive histone markers at select gene promoters and improve behaviors associated with side effect severity and cognition in mice treated with antipsychotics. This central hypothesis has been summarized in Figure 1.

While co-treatment of elderly patients with antipsychotics and adjunct HDACis is intriguing, there are still numerous open questions that should preclude physicians from early adoption of this strategy. These questions include relative unknowns about the risk of side effects, such as increased adverse cardiovascular events, and long-term efficacy. Another important consideration involves the use of antipsychotics in particular subgroups of elderly patients, especially those with dementia and BPSD. Studies that evaluate these drugs specifically in dementia patients are of great value for future translation. Additionally, from a scientific perspective, much remains to be revealed concerning the full extent of epigenetic changes and antipsychotic function. First of all, we need to determine whether the observed effects in typical antipsychotics with adjunct HDACis can be extended to atypical antipsychotics. Nonetheless, we suggest that adjunct epigenetic modifiers hold great promise for the treatment of elderly patients with antipsychotics and hope other researchers, pharmacists, and physicians will continue to unravel the intricate interplay between epigenetic alterations, aging, and antipsychotic action.

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Figure 1. Proposed Schematic of Aging-Induced Epigenetic Alterations and Their Effect on Antipsychotic Action

The flow diagram summarizes the central hypothesis in this review. Although the novel epigenetic mechanisms presented here have been partially evaluated, additional investigations of these mechanisms are necessary in the future. APDs: antipsychotic drugs; HDACi: histone deacetylases inhibitor, CYPs: cytochrome p450; ABC: ATPases binding cassette