Psychotropic Drug Effects on Gene Transcriptomics Relevant to Alzheimer Disease

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Abstract: Psychotropics are widely prescribed in Alzheimer disease (AD) without regard to their pathobiological effects. Results summarize a comprehensive survey of psychotrophic effects on messenger ribonucleic acid (mRNA) expression for 52 genes linked to AD. Pending future investigations, current data indicate that atypical antipsychotics, lithium, and fluoxetine reduce AD risk, whereas other drug classes promote risk. Risk may be attenuated by antipsychotics and lithium (down-regulate TNF), atypical antipsychotics (down-regulate TF), risperidone (down-regulates IL1B), olanzapine (up-regulates TFAM, down-regulates PRNP), fluoxetine (up-regulates CLU, SORCS1, NEDD9, GRN, and ECE1), and lithium coadministered with antipsychotics (down-regulates IL1B).

METHODS

The author comprehensively surveyed gene expression as a function of psychotropic treatment for genes associated with AD risk, classic AD mutations, and those of select interest in AD by assessing literature in the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) and data in the Gene Expression Omnibus Profiles database (GEO Profiles, http://www.ncbi.nlm.nih.gov/sites/entrez?db=geo) during the month of June, 2010. Associated genes consisted of the 42 genes most strongly associated with AD according to the Alzheimer Research Forum database2 (updated October 11, 2010): APOE e2/3/4, CLU, PICALM, EXOC3L2, BIN1, CR1, SORL1, GWA_14q32.13, TNK1, IL8, LDLR, CST3, hCG2039140, CHRNB2, SORCS1, TNF, CCR2, ACE, DAPK1, GAB2, TF, PCDH11X, MTHFR, LOC651924, OTC, ADAM10, NEDD9, CH25H, IDE, LOC439999, GRN, IL33, IL1B, PGBD1, THRA, CALHM1, ENTPD7, TFAM, IL1A, ECE1, PRNP, and GAPDH. Classic AD mutations included amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Genes of select interest included ESRI, secretases [α, β (BACE), and γ], phosphatases PPP3R1 and PION, and the sirtuin SIRT1. Genes were searched in PubMed by their official symbol, official name, gene identification number, aliases, and, where appropriate, loci. A search of the official symbol alone proved to be the most effective search strategy in GEO profiles.

Drugs considered included first-line antipsychotics, mood stabilizers, antidepressants, anxiolytics, and dextromethorphan combined with quinidine. Drugs were searched by their psychopharmacological category and by their specific names in each database. A variety of paradigms and treatment durations were encountered. Because psychotropics tend to be administered chronically in the clinical treatment of AD, only reports of chronic administration (at least 3 wk duration in animal studies) are considered here.

Gene expression data in GEO Profiles were considered if a given treatment was compared with untreated controls under the same experimental conditions and if the data involved at least 2 determinations at a single locus. Gene expression data were found for the selective serotonin reuptake inhibitor antidepressant fluoxetine, the neuroleptic atypical antipsychotic haloperidol, and the atypical antipsychotics olanzapine and clozapine. Fluoxetine was administered for 21 days in mice and gene expression was determined relative to untreated controls in the hippocampus (GEO Profiles accession number GDS2803)3 using the Affymetrix Gene Chip Mouse Genome 430 2.0 Array. Rats treated with olanzapine for 21 days were compared with untreated...
controls and gene expression was determined in frontal cortex (accession number GDS2608) using the Affymetrix Gene Chip Rat Genome 230 2.0 Array. Results for haloperidol and clozapine relative to untreated control mice reflect gene expression in brain after treatment for 4 weeks (accession number GDS2537) using the Affymetrix Gene Chip Murine Genome U74 Version 2 Array (MG_U74Av2) and 12 weeks (accession number GDS2531) using the Affymetrix Gene Chip Mouse Expression 430A Array (MOE430A). In contrast to dextromethorphan, data for quinidine were present in GEO Profiles, but not for the genes considered in this study. These normalized expression data were derived from a gene chip and remain to be confirmed by quantitative real-time polymerized chain reaction (RT-PCR) or other analyses.

To provide a measure of statistical guidance, GEO Profiles data were analyzed by a 1-way analysis of variance (ANOVA) with Bonferroni correction. The results of database searches in PubMed and GEO Profiles were summarized for each gene. There were determinations of gene expression in GEO Profiles for murine homologues of the genes of interest as affected by fluoxetine, olanzapine, haloperidol, and clozapine in most cases. Reporting of findings is limited to genes where specific probe sets were up-regulated or down-regulated by 20%. Percentage change for a given reporter probe set was calculated as the difference of the reporter probe value for treated animals from its untreated control values divided by that control value. In cases where there were positive findings for any gene probe set, probe sets were assessed to determine their reliability in assaying gene expression. Results are provided for genes for which changes in expression were observed after considering probe set reliability.

RESULTS

PubMed revealed no relevant gene expression data for APOE, CLU, PICALM, EXOC3L2, BIN1, CR1, SORL1, GWA 14q32.13, TNK1, IL8, LDLR, CTH3, hCG2039140, CHRN8B2, SORCS1, ACE, DAPK1, GAB2, PCDH11X, MTHFR, LOC651924, OTC, ADAM10, NEDD9, CH25H, IDE, LOC439999, GRN, IL33, IL1B, PGBD1, THRA, CALHM1, ENTPD7, TFAM, IL1A, ECE1, PRNP, GAPDH, APP, PSEN1, PSEN2, 3×-secretase, BACE1, γ-secretase, ESRe, PPP3R1, PION, or SIRT1. GEO Profiles revealed no gene expression data for GWA 14q32.13, hCG2039140, PCDH11X, LOC651924, LOC439999, IL33, IL1B, PGBD1, CALHM1, γ-secretase, or γ-secretase.

Although expression data were available in GEO Profiles, data analysis demonstrated no appreciable effects by fluoxetine, haloperidol, olanzapine, or clozapine on APOE, PICALM, EXOC3L2, BIN1, CR1, TNK1, IL8, LDLR, CTH3, CHRN8B2, TFAM, CCR2, ACE, DAPK1, GAB2, TF (transferrin, 3q22.1) transfers iron and may play a role in oxidative stress. The C570T mutation in the C2 allele replaces proline for serine in TF, promoting accumulation of redox-active iron and producing oxidative stress in neurons. In PubMed, neuroleptic treatment in patients with schizophrenia was associated with up-

Associated Genes

CLU (clusterin located on chromosome 8 at p21-p12) has been linked to AD. Clusterin appears to be a chaperone protein that may also act to stabilize stressed protein structures. It is capable of binding β-amyloid (Aβ) peptides and fibrils to promote endocytosis and prevent fibrillization. It further can prevent complement activation, regulate cholesterol and lipid metabolism, and bind the apoptotic Bax protein; however, a variant isofrom can translocate to the nucleus and induce apoptosis. In GEO Profiles, fluoxetine up-regulated mouse hippocampal Clu by a factor of 1.33 (ie, 33% increase in Clu mRNA expression) at probe set 1454849_x_at (NCBI refseq refBB433678), 1.26 at 1437458_x_at (AV075715), and 1.27 at 1418626_a_at (NM_013492), the best supported probe sets with the highest identities, but only 1.08 at 1437689_x_at (AV152288), the least well supported with the lowest identity.

SORCS1 (sortilin-related VPS10 domain containing receptor 1, 10q23 to 10q25) has been associated with AD, especially in women, particularly the rs17277986 polymorphism located in a presumably functional region of the gene. SORCS1, a substrate of γ-secretase, may inhibit this enzyme and thereby reduce Aβ peptide processing. As the rs17277986 polymorphism may reduce SORCS1 function at intron 1.9 In GEO Profiles, chronic fluoxetine up-regulated Sorcs1 by a factor of 2.44 at 1436662_at (BB002723) and 1.73 at 1425864_a_at (AF284755) but not at the less well-supported 1421590_at (1.09, NM_021377).

TNF (tumor necrosis factor, 6p21.3) elevations are associated with both AD risk and AD itself. It correlates with cognitive and behavioral disturbances in AD. The TNFR1 receptor is required for Aβ-mediated neuronal death in AD, and TNF-α receptor binding affinity increases in AD. In 3×TgAD mice, inhibition of soluble TNF reduced neuroinflammatory effects on pre-plaque pathology. An open-label clinical trial of the TNF-α inhibitor etanercept was associated with clinical improvement in AD. Thus, there is evidence that increased TNF gene expression may promote AD. Chronic treatment of patients with bipolar disorder with lithium carbonate or antipsychotic treatment each independently down-regulated monocytic TNF mRNA expression compared with bipolar patients not treated for over 12 months. CCR2 (chemokine (C-C motif) receptor 2, 3p21.3) may protect against AD risk since Ccr2-deficient APP transgenic mice showed increased brain Aβ levels and impaired mononuclear phagocyte migration. In PubMed, a study of patients with bipolar disorder found that neither lithium nor antipsychotics had a demonstrable effect on CCR2 mRNA expression after chronic treatment. TF (transferrin, 3q22.1) transfers iron and may play a role in oxidative stress. The C570T mutation in the C2 allele replaces proline for serine in TF, potentially promoting accumulation of redox-active iron and producing oxidative stress in neurons.
regulated TF mRNA in postmortem brain, whereas atypical antipsychotics down-regulated it relative to patients with schizophrenia who were untreated.22

NEDD9 (neural precursor cell expressed, developmentally down-regulated 9, 6p25 to 6p24) is an adhesion docking protein involved in neurite development.23 The rs760678 polymorphism associated with late-onset AD involves a region of TATA-binding and GATA-binding motifs for transcription factors, and a loss of function would reduce physiological reserve after neuronal loss and compromise regeneration.23 In GEO Profiles, fluoxetine up-regulated Nedd9 expression by a factor of 1.45 at 1422818_at (NM_017464), 1.37 at 1450767_at (NM_017464), 1.71 at 1437132_x_at (BB535494), and 1.00 at 1447885_x_at (BB45068).

GRN (granulin, 17q21.32) is involved in neurite outgrowth and neuronal survival.24,25 Loss-of-function mutations in this gene have been associated with phenotypic AD although most cases have represented frontotemporal lobar degeneration with ubiquitin inclusions at autopsy.26–30 Alleles associated with reduced GRN are also associated with histopathological AD.25 GRN genotype may convey risk for AD in a sex-specific manner, with the polymorphisms rs4792939, rs850713, and rs5848 posing risk in males.24 In GEO Profiles, fluoxetine up-regulated Grn expression compared with those not treated for over 12 months; however, neither class of drug by itself significantly down-regulated IL1B mRNA.18 In PubMed, peripheral monocytes from patients with schizophrenia had increased IL-1β mRNA expression and increased serum levels, decreased by 4 weeks of risperidone treatment.38 Collectively, chronic lithium carbonate together with antipsychotic treatment down-regulated monocyte IL1B mRNA expression in treated patients with bipolar disorder compared with those not treated for over 12 months; however, neither class of drug by itself significantly down-regulated IL1B mRNA.38 In rats, however, chlorpromazine, haloperidol, imipramine, maprotiline, fluvoxamine, and diazepam for 28 days increased Il1b mRNA in several brain areas by RT-PCR.39

THRA (thyroid hormone receptor, 17q11.2) message is reduced by half in CA1 hippocampal neurons in AD compared with controls having Huntington disease.40 If THRA down-regulation and reduced function genotypes are involved in AD pathophysiology, then up-regulation might prove to be therapeutic. In GEO Profiles, olanzapine down-regulated Thra in rat frontal cortex by a factor of 0.80 (ie, 20% reduction in Thra mRNA expression) at 1367726_at (NM_031134), the only probe set of 3 that was not compromised by lack of detection call.

TFAM (mitochondrial transcription factor A, 10q21) is required for transcription and replication of mitochondrial DNA. Overexpression of TFAM in SH-SY5Y neuroblastoma cells protected mitochondria against Aβ42 oxidative stress, improved energy production, and attenuated apoptosis.41 The missense polymorphism S12T has been found to be an AD risk factor in a Spanish population.42 Thus, reduced expression may promote AD neurodegeneration. In GEO Profiles, olanzapine up-regulated TfiA by a factor of 1.26 at 1367941_at (NM_031326, the only probe set investigated).

IL1A (interleukin 1α, 2q14) is a proinflammatory factor conferring risk in AD and other neurodegenerative diseases, which is increased in AD pathology. In GEO Profiles, olanzapine up-regulated Tfam expression by a factor of 1.42 at 1438629_x_at (AV166504), 1.34 at 1456567_x_at (BB000455), and 1.24 at 1448148_at (M66736).

TABLE 1. Putative Effects of Psychotropics on Alzheimer Disease Risk by Gene

<table>
<thead>
<tr>
<th>Rank</th>
<th>Gene</th>
<th>Chronic Drug Effects On Gene mRNA and AD Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>CLU</td>
<td>Fluoxetine up-regulates—may reduce risk (except in pro-apoptotic variant isoform)</td>
</tr>
<tr>
<td>15</td>
<td>SORCS1</td>
<td>Fluoxetine up-regulates—may reduce risk (except in rs17277986 polymorphism)</td>
</tr>
<tr>
<td>16</td>
<td>TNF</td>
<td>Antipsychotics and lithium down-regulate—may reduce risk</td>
</tr>
<tr>
<td>21</td>
<td>TF</td>
<td>Atypical antipsychotics down-regulate—may reduce risk, especially in C570T C2 mutations</td>
</tr>
<tr>
<td>21</td>
<td>TF</td>
<td>Neuroleptics up-regulate—may increase risk, especially in C570T C2 mutations</td>
</tr>
<tr>
<td>27</td>
<td>NEDD9</td>
<td>Fluoxetine up-regulates—may reduce risk (except in rs760678 polymorphism)</td>
</tr>
<tr>
<td>31</td>
<td>GRN</td>
<td>Fluoxetine up-regulates—may reduce AD and FTLDU risks (may increase risk in risk-associated polymorphisms in males)</td>
</tr>
<tr>
<td>33</td>
<td>IL1B</td>
<td>Risperidone and antipsychotic-plus-lithium down-regulate—may reduce risk, especially in +3953 polymorphism T and TT genotypes</td>
</tr>
<tr>
<td>33</td>
<td>IL1B</td>
<td>Chlorpromazine, haloperidol, imipramine, maprotiline, fluvoxamine, and diazepam up-regulate—may increase risk (especially in +3953 polymorphism T and TT genotypes)</td>
</tr>
<tr>
<td>35</td>
<td>THRA</td>
<td>Olanzapine down-regulates—may increase risk</td>
</tr>
<tr>
<td>38</td>
<td>TFAM</td>
<td>Olanzapine up-regulates—may reduce risk (except in S12T polymorphism)</td>
</tr>
<tr>
<td>39</td>
<td>IL1A</td>
<td>Olanzapine up-regulates—may increase risk (especially in –889 polymorphism genotypes)</td>
</tr>
<tr>
<td>40</td>
<td>ECE1</td>
<td>Fluoxetine up-regulates—may reduce risk</td>
</tr>
<tr>
<td>41</td>
<td>PRNP</td>
<td>Olanzapine down-regulates—may increase risk in early AD and in codon 129 genotypes</td>
</tr>
<tr>
<td></td>
<td>PION</td>
<td>Haloperidol up-regulates—may increase risk</td>
</tr>
</tbody>
</table>

Effects of specific drugs on gene mRNA expression and their presumptive effects on AD risk are displayed. (PION is not ranked and is a gene of select interest).

AD indicates Alzheimer disease; FTLDU, frontotemporal lobar degeneration with ubiquitin inclusions.
TABLE 2. Putative Effects of Psychotropics on Alzheimer Disease Risk Genes by Drug

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>May reduce risk by effects on TF (21)</th>
<th>May increase risk by effects on TF (21)</th>
<th>May increase risk by effects on IL1B (33)</th>
<th>May increase risk by effects on IL1B (33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics—reduce risk (but depends on drug)</td>
<td>May reduce risk by effects on TNF (16)</td>
<td>Chlorpromazine—increases risk</td>
<td>Haloperidol—increases risk</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Neuroleptics—increase risk</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>Olanzapine—increases risk</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Atypical Antipsychotics—reduce risk</td>
<td>Olanzapine—increases risk</td>
<td>May reduce risk by effects on TF (21)</td>
<td>May increase risk by effects on TF (21)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Antipsychotics-plus-lithium</td>
<td>May reduce risk by effects on TF (21)</td>
<td>May increase risk by effects on TF (21)</td>
<td>May increase risk by effects on TF (21)</td>
<td>May increase risk by effects on TF (21)</td>
</tr>
<tr>
<td>Antipsychotics-plus-lithium—reduces risk</td>
<td>May reduce risk by effects on TF (21)</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>May reduce risk by effects on TNF (16)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Antidepressants-plus-lithium</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Antidepressants-plus-lithium—reduces risk</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium—reduces risk</td>
<td>May reduce risk by effects on TNF (16)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Antipsychotics-plus-lithium</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
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<tr>
<td>Antidepressants-plus-lithium</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
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<tr>
<td>Antidepressants-plus-lithium—reduces risk</td>
<td>May reduce risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
<td>May increase risk by effects on IL1B (33)</td>
</tr>
</tbody>
</table>

Each gene is followed by its ranking for AD risk, such that the lower the number, the greater its potential effect on AD risk. The greater the number, the less is the potential effect on AD risk. (PON is not currently ranked and is a gene of select interest.) These findings may not apply to patients with mutations and variants, particularly the CLU proapoptotic variant isoform, TF C370T C2, IL1B +393T, IL1A —889, and PRNP codon 129, all of which are associated with increased AD risk in GEO Profiles, olanzapine down-regulated the expression of Prnp by a factor of 0.75 at 1370156_at (B1278802).

Classical Mutations

There were no relevant results for APP, PSEN1, or PSEN2 in PubMed and no appreciable changes in gene expression in GEO Profiles.

Genes of Select Interest

PI3K (phosphatase involved in tau dephosphorylation) and was recently found to be a novel activator of γ-secretase (GSAP) without Notch interaction. In this study, GSAP (Pion) knockdown mice evidenced decreased β-amyloid levels and amyloid plaque development. GEO Profiles indicated that haloperidol administered for 12 weeks up-regulated Pion by a factor of 1.28 by probe set 1427515_at (BB637972), the only probe set evaluated. Although it is possible that haloperidol may reduce AD progression or risk, the effect of GSAP expression on human AD progression and risk remains to be demonstrated.

DISCUSSION

Enthusiasm for the application of these results must be tempered by limitations including associations of these genes with AD in some populations or genotypes but not in others, changing risk rankings of genes over time, a relatively early literature, the paucity of gene expression data after chronic treatment, site-specific expression in only certain brain regions, temporal specific expression corresponding to only specific treatment durations, an uncertain translation of murine gene expression to humans with AD, and an evolving understanding of gene roles in AD pathogenesis. Some genes may have the capacity to exert both neuroprotective and prodegenerative effects in AD and could presumably act differentially in different populations or at different stages of AD. Moreover, some drugs regulate the expression of multiple genes, simultaneously producing both neuroprotective and prodegenerative effects. The gene chip data taken from GEO Profiles is limited by the large number of genes evaluated (potential for Type I error), the small number of determinations of gene expression for each drug, the absence of quantitative confirmation (e.g., RT-PCR) and replication, and the absence of statistical significance for a 20% change in expression in GEO Profiles, precluding statistical analyses of these data. Furthermore, differential effects of gene expression may obtain at different stages of AD. A given gene product may function neuroprotectively at one stage of the disease, yet contribute to pathological progression at another. For example, olanzapine’s effects on PRNP may promote apoptosis and inhibit neurogenesis early in the disease yet deter neurodegenerative plaque formation later in the disease. Nevertheless, against this backdrop, present observations allow some consideration of the potential effects of psychotropic drugs on AD-relevant genes and, conceivably, perhaps AD risk and progression.

The data suggest that a variety of psychotropics commonly employed in AD treatment may affect AD risk or progression by affecting gene expression. Table 1 summarizes the putative effects of psychotropic treatment duration of at least 21 days on AD risk. Table 2 summarizes these effects that...
by drug and constitutes an initial summary of the data that is necessarily incomplete owing to the current early state of the literature (eg, evolving risk associations, gene definitions, related probe sets, expression data, and gene functions that will likely change over time). In general, atypical antipsychotics, lithium, and fluoxetine appeared to be generally protective whereas most antipsychotics, antidepressants, and diazepam tended to be deleterious in AD. In contrast, patients with mutations or select variants of cer-

### TABLE 3. Statistical Analysis of Gene Data in GEO Profiles

<table>
<thead>
<tr>
<th>Gene</th>
<th>Probe Set</th>
<th>Mean ± SD (Controls)</th>
<th>Mean ± SD (Treated)</th>
<th>F Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLU</td>
<td>1454849_x_at</td>
<td>16325.4 ± 439.36</td>
<td>21705.5 ± 977.78</td>
<td>50.378</td>
<td>0.0193</td>
</tr>
<tr>
<td>SORCS1</td>
<td>1436662_x_at</td>
<td>88.192 ± 19.079</td>
<td>215.449 ± 27.044</td>
<td>5716.44</td>
<td>0.000175*</td>
</tr>
<tr>
<td>NEDD9</td>
<td>1422818_x_at</td>
<td>12.020 ± 2.993</td>
<td>20.813 ± 1.877</td>
<td>12.39</td>
<td>0.0721</td>
</tr>
<tr>
<td>PRNP</td>
<td>1370156_at</td>
<td>13911.7 ± 2330.27</td>
<td>10374.0 ± 759.766</td>
<td>8.333</td>
<td>0.0278</td>
</tr>
<tr>
<td>THRA</td>
<td>1367726_at</td>
<td>606.741 ± 121.385</td>
<td>486.514 ± 77.006</td>
<td>2.798</td>
<td>0.14541</td>
</tr>
<tr>
<td>TFAM</td>
<td>1367941_at</td>
<td>305.941 ± 122.847</td>
<td>385.685 ± 167.068</td>
<td>0.592</td>
<td>0.47102</td>
</tr>
<tr>
<td>IL1A</td>
<td>1371170_x_at</td>
<td>89.560 ± 9.572</td>
<td>108.190 ± 67.122</td>
<td>0.151</td>
<td>0.735</td>
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<tr>
<td>ECE1</td>
<td>1448148_at</td>
<td>578.231 ± 11.345</td>
<td>716.103 ± 56.462</td>
<td>11.462</td>
<td>0.0773</td>
</tr>
<tr>
<td>PION</td>
<td>1457541_x_at</td>
<td>533.629 ± 14.967</td>
<td>455.829 ± 5.079</td>
<td>83.619</td>
<td>0.01175</td>
</tr>
</tbody>
</table>

**Fluoxetine effects on CLU, NEDD9, and GRN** in GEO Profiles remained significant after Bonferroni correction (Table 3), however, a dismissal of other findings as noise on the basis of statistical significance could potentially cause a Type II error because of the large number of genes surveyed here, resulting in the exclusion of gene effects that may ultimately be found to play a role in AD management upon more specific analyses of the nigrostriatal system with RT-PCR. On the other hand, another caveat is that the _x_at probe sets can cross-hybridize in an unpredictable manner, and all 3 probe sets surviving Bonferroni correction were of this type.

It is difficult to predict the net effects of these drugs on AD risk, which may vary with AD stage and the individual patient’s genomics. Genes of highest rank order (indicating strongest evidence of association) might more potently affect risk and pathogenesis than those of lower rank order. Another potential variable is the relative potency of influence of a drug on the expression of a given gene (eg, 500% vs. 20% up-regulation). It is possible that a highly potent effect on a weakly associated risk gene might overwhelm weak effects on strongly associated genes. It is also possible that just because a gene is associated with AD does not mean that modification of that gene’s expression will necessarily modify AD risk.

Certain caveats regarding these preliminary findings deserve particular emphasis. First, as noted above, changing rankings in risk genes over time indicate the need to confirm the quantitative risk associations of the genes considered here in future studies because new risk genes may emerge while previously associated genes may not be confirmed. Second, it is always possible that a literature search may fail to detect some studies, and some findings detected by the search can be of uncertain relevance. A study of psychotropic effects on APOE in malignant cell lines was detected but not included in the Results because the findings may or may not be obtained in nonmalignant tissues. Third, the impact of psychotropics on AD risk may be relatively small and should be cautiously interpreted as, besides CLU effects on other top ranked risk genes were not evident, in contrast to effects on genes with lower risk rankings. Fourth, as noted above, transcription effects in animals, especially rodents, may not be expressed the same way in humans. Fifth, diffuse epigenetic effects may also occur with some psychotropics, further affecting transcription. For example, valproate is an H3 histone deacetylase inhibitor and 4-week treatment can epigenetically affect the transcription of multiple genes by this mechanism, specifically in AD. Sixth, gene–gene interactions may potentially limit or even outweigh the transcription effects reviewed here, for example genes associated with AD neuropsychiatric features and AD-associated cerebrovascular atherosclerosis. Neuropsychiatric features are a major source of morbidity and caregiver burden in AD, and the usual impetus for administering psychotropics, and have been related to neurotransmitter system genes. Their treatment could therefore conceivably alter these genes, which in turn may influence the transcription of other genes, potentially including AD risk genes. Similarly, antipsychotics influence cerebrovascular risk, potentially affecting atherosclerosis genes, which in turn influence AD risk, either pathophysiologically or through modifying AD risk gene expression. Finally, the effects of psychotropics on AD-associated genes have not been systematically studied and much remains to be learned. Thus, the present results must be considered preliminary in light of the above.
There are of course many other effects of psychotropics that can impact multiple processes at the neuronal level, and gene expression is only one of many of these processes that can influence neurodegenerative outcome. Even if psychotropic effects on gene transcription are found to account for a significant amount of the variance in neuroprotective effect, important constraining variables may involve posttranslational effects in the neuropathological process, stage of illness, and the overall genetic context of the individual patient. For example, although antidepressants seem to promote AD risk could potentially overwhelm salutary mRNA effects. Conversely, although antidepressants seem to promote AD risk at the level of the transcriptome, these drugs have many downstream neuroprotective effects that may countermand mRNA effects. In any event, this report provides an initial framework by which to understand the potential impact of commonly prescribed drugs on genes that are relevant to AD. The effects of psychotropics on the expression of these genes should now be studied using RT-PCR, particularly in the hippocampus, basal nucleus of Meynert, and relevant cortices in AD, and in affected brain regions in frontotemporal lobar degeneration and other dementias.

REFERENCES


