Abstract: Objectives: Psychotropic drugs are widely prescribed in Parkinson's disease (PD) without regard to their pathobiological effects, and these drugs affect the transcription of a large number of genes. Effects of these drugs on PD risk gene transcription were therefore surveyed. Methods: Results summarize a comprehensive survey of psychotropic effects on messenger ribonucleic acid (mRNA) expression evident in published data for 70 genes linked to PD risk. Results: Psychotropic drugs can meaningfully affect PD risk gene mRNA transcription, including antipsychotics (upregulate dopamine receptors D2 and D3 (DRD2, DRD3); downregulate low-density lipoprotein receptor-related protein 8 (LRP8), ubiquitin carboxyl-terminal esterase L1 (UCHL1, also known as PARK5)), haloperidol (upregulates DRD3, parkin (PRKN, also known as PARK2), DRD2; downregulates brain-derived neurotrophic factor (BDNF)), risperidone (upregulates monoamine oxidase B (MAOB), DRD2), olanzapine (upregulates transmembrane protein 163 (TMEM163), BDNF, glutathione S-transferase mu 1 (GSTM1), MAOB, DRD2, solute carrier organic anion transporter family, member 3A1 (SLCO3A1)), aripiprazole (upregulates DRD2), quetiapine, paliperidone, lurasidone, carbamazepine, and many antidepressants (upregulate BDNF), lithium and bupropion (downregulate BDNF), amitriptyline (upregulates DRD3, DRD2), imipramine (upregulates BDNF, DRD3, DRD2), desipramine (upregulates BDNF, DRD3), and fluoxetine (upregulates acid beta-glucosidase (GBA), coiled-coil domain containing 62 (CCDC62), BDNF, DRD3, UCHL1, unc-13 homolog B (UNC13B), and perhaps huntingtin interacting protein 1 related (HIP1R); downregulates microtubule-associated protein tau (MAPT), methylcrotonoyl-coenzyme A carboxylase I (MCCC1), GSTM1, 28kDa calbindin 1 (CALB1)). Fluoxetine effects on BDNF and UCHL1 in GEO Profiles were statistically robust. Conclusions: This report provides an initial summary and framework to understand the potential impact of psychotropic drugs on PD-relevant genes. Antipsychotics and serotoninergic antidepressants may potentially attenuate PD risk, and lithium and bupropion may augment risk, through MAPT, GBA, CCDC62, HIP1R, BDNF, and DRD2 transcription, with MAPT, GBA, and CCDC62 being strongly associated with PD risk in recent meta-analyses. Limitations of these findings and a research agenda to better relate them to the nigrostriatum and PD are discussed.

Response to Reviewers: Response to Reviewer #1 comment: Thank you for your decision to accept the manuscript for publication.
Response to Reviewer #2 comment: Thank you for your decision to accept the manuscript for publication.

Response to Reviewer #3 comment No. 1: Thank you for your clarification regarding the comparison to diabetes/obesity genes. I am glad to learn that I had correctly interpreted your comment. I think that your idea to consider these genes is a good one, providing an "external control" of sorts.

Response to Reviewer #3 comment No. 2: In an effort to make the manuscript more clear and concise, I have once again gone back over the manuscript. It is now shortened by 242 words. The manuscript is now as clear as I know how to make it absent specific suggestions. I hope that it will now be acceptable.

Response to Reviewer #3 comment No. 3: I have deleted the former diabetes paragraph and distilled its contents into 2 sentences (paragraph 3 of Discussion).
March 26, 2012

Professor Guy Drolet  
Editor  
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Dear Professor Drolet,

I am re-submitting the manuscript entitled "Psychotropic Drug Effects On Gene Transcriptomics Relevant To Parkinson's Disease," revised as requested.

Although Reviewers #1 and #2 have now approved of the manuscript (please see your original March 21 letter to me below), Reviewer #3 commented: “After all, from the whole description, the manuscript basically can be acceptable. However, I would like to suggest the author to revise the manuscript carefully and make it more clear and concise. I don't think diabetes paragraph which the author added in the revision is needed. The author should use one or two sentences to briefly address his point since the diabetes results are not the key results for the whole paper.”

In response to the Reviewer’s request, I have distilled the diabetes paragraph into 2 sentences (see immediately below this letter). I have once again gone back over the manuscript seeking to make it still more concise and clear. It is now shortened by 242 words. The manuscript is now as clear as I know how to make it absent specific suggestions. I hope that it will now be acceptable.

In that event, I suspect that there will be a risk in copy-editing to make changes that would seem consistent with style rules but that will result in inaccuracies. For example, genes in humans are designated in capital letters (e.g., “BDNF”) whereas the gene in rats or mice is given in lower case (e.g., “Bdnf”). Also, the names of probesets are terms such as “1450099_a_at” etc., that could appear to be typographical errors or incomplete sentences. Further, reporter names include terms such as “NM_008094” and “BB241507” that might also appear to be typographical errors or inconsistencies. I have taken pains to use the nomenclature and terms of art in an accurate fashion, and I believe that there will be very little need for revision by copy editors. To save both them and myself a lot of extra trouble, would you please convey this to them and ask that they query me before making changes that we will only have to change back to their original form?

Thank you for the opportunity to revise this manuscript. I trust that this revision addresses all concerns and I look forward to learning the results of the review.

Sincerely,
2 Sentence Version Of Former Diabetes Paragraph

Clearly, PD–associated genes are not the only genes affected by psychotropics, and transcriptional explorations in GEO Profiles of leading genes associated with type II diabetes mellitus and antipsychotic–induced diabetes and weight gain (TCF7L2, PPARG, KCNJ11, IGF2BP2, HHEX, CDKAL1, SLC30A8, FTO, CNR1) revealed that IGF2BP2 exceeded the 20% threshold and was upregulated by a factor of 1.31 (Lim et al. 2010 http://t2db.khu.ac.kr:8080/; Irvin et al. 2009; Tiwari et al. 2010; Tiwari et al. 2011; Vehof et al. 2011). This is comparable to the transcriptional changes observed in the present study, instilling confidence that PD gene expression induced by psychotropics can potentially affect PD onset and progression in a clinically meaningful manner.
Highlights

- Psychotropics are widely used in treating Parkinson’s disease (PD)
- Initial evidence indicates these psychotropics can affect PD risk-gene transcription
- Further study of PD risk-gene transcription in PD clinical models is warranted
- Studies should focus on psychotropic – related modification of PD risk and progression
Psychotropic Drug Effects On Gene Transcriptomics Relevant To Parkinson’s Disease

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Running Head: Psychotropic Effects On PD Transcriptomics

Conflicts of Interest and Source of Funding: None for either
Abstract

Objectives: Psychotropic drugs are widely prescribed in Parkinson’s disease (PD) without regard to their pathobiological effects, and these drugs affect the transcription of a large number of genes. Effects of these drugs on PD risk gene transcription were therefore surveyed. Methods: Results summarize a comprehensive survey of psychotropic effects on messenger ribonucleic acid (mRNA) expression evident in published data for 56-70 genes linked to PD risk. Results: Psychotropic drugs can meaningfully affect PD risk gene mRNA transcription, including antipsychotics (upregulate dopamine receptors D2 and D3 (DRD2, DRD3); downregulate low-density lipoprotein receptor-related protein 8 (LRP8), ubiquitin carboxyl-terminal esterase L1 (UCHL1, also known as PARK5)), haloperidol (upregulates DRD3, parkin (PRKN, also known as PARK2), DRD2; downregulates brain-derived neurotrophic factor (BDNF)), risperidone (upregulates monoamine oxidase B (MAOB), DRD2), olanzapine (upregulates transmembrane protein 163 (TMEM163), BDNF, glutathione S-transferase mu 1 (GSTM1), MAOB, DRD2, solute carrier organic anion transporter family, member 3A1 (SLCO3A1)), aripiprazole (upregulates DRD2), quetiapine, paliperidone, lurasidone, carbamazepine, and many antidepressants (upregulate BDNF), lithium and bupropion (downregulate BDNF), amitriptyline (upregulates DRD3, DRD2), imipramine (upregulates BDNF, DRD3, DRD2), desipramine (upregulates BDNF, DRD3), and fluoxetine (upregulates acid beta-glucosidase (GBA), coiled-coil domain containing 62 (CCDC62), BDNF, DRD3, UCHL1, unc-13 homolog B (UNC13B), and perhaps huntingtin interacting protein 1 related (HIP1R); downregulates microtubule-associated protein tau (MAPT), methylcrotonyl-coenzyme A carboxylase I (MCCC1), GSTM1, 28kDa calbindin 1 (CALB1)). Fluoxetine effects on BDNF and UCHL1 in GEO Profiles were statistically robust. Conclusions: This report provides an initial summary and framework to understand the potential impact of psychotropic drugs on PD-relevant genes. Antipsychotics and serotonergic antidepressants may potentially attenuate PD risk, and lithium and bupropion may
augment risk, through MAPT, GBA, CCDC62, HIP1R, BDNF, and DRD2 transcription, with MAPT, GBA, and CCDC62 being strongly associated with PD risk in recent meta-analyses. Limitations of these findings and a research agenda to better relate them to the nigrostriatum and PD are discussed.

Key Words: Parkinson’s disease, antipsychotics, antidepressants, gene expression, mRNA, risk

1.0 Introduction
Neuropsychiatric conditions occur in more than half of patients with Parkinson’s disease (PD) and exact significant morbidity (Lauterbach, 2005, 2004). Among these conditions, psychotic, mood, and anxiety disorders figure prominently. Psychotic symptoms occur in up to 50%, manic symptoms in 10%, and both are treated with antipsychotics. Depressive and anxiety disorders each occur in at least 40% of PD patients, and both are treated with antidepressants.

Additionally, anxiety disorders and sleep disorders, which have been documented in up to 90% of patients with PD, are treated with anxiolytics and, at times, antihistaminic agents (Lauterbach, 2005, 2004). Thus, psychotropics are commonly used to treat these conditions although the effects of these drugs on PD pathobiology are not well known (Lauterbach et al., 2010b).

A large number of genes have been implicated in the risk and pathogenesis of PD, and ongoing meta-analyses are determining their statistical associations. Psychotropics can affect the expression of many genes and, therefore, potentially the expression of genes involved in PD.

The author was therefore interested in the effects of these drugs on the expression of genes associated with PD (specifically, mutations, risk genes, and genes of interest) and explored these
effects in National Library of Medicine published medical literature and gene expression databases. As this is a relatively nascent and emerging literature, it was anticipated that there might be a number of limitations to the data, but that some early clues might be gleaned that could serve to inform and direct future research efforts. The goal of this survey, then, was to examine the potential of first-line psychotropics available in the United States, drugs that are frequently employed in the management of PD, to influence the expression of genes catalogued in a PD risk gene database that are either statistically or pathobiologically implicated in PD risk.

More specifically, these first line psychotropics involved the following drug categories and specific drugs: neuroleptic, atypical antipsychotic, antipsychotic, antidepressant, tricyclic antidepressant, heterocyclic antidepressant, selective serotonin reuptake inhibitor, SSRI, anxiolytic, benzodiazepine, pramipexole, ropinirole, amantadine, haloperidol, fluphenazine, trifluoperazine, thiothixene, chlorpromazine, thioridazine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, clozapine, paliperidone, iloperidone, asenapine, lurasidone, tetrabenazine, pimavanserin, lithium, carbamazepine, oxcarbazepine, valproate, lamotrigine, amitriptyline, imipramine, nortriptyline, desipramine, clomipramine, trimipramine, doxepin, protriptyline, maprotiline, bupropion, fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram, s-citalopram, trazodone, nefazodone, venlafaxine, duloxetine, mirtazapine, atomoxetine, buspirone, diazepam, chlordiazepoxide, flurazepam, temazepam, chlorazepate, clonazepam, lorazepam, oxazepam, alprazolam, zaleplon, zolpidem, zopiclone, s-zopiclone, cyproheptadine, hydroxyzine, diphenhydramine, benztropine, trihexyphenidyl, modafinil, ramelteon, dextromethorphan, and quinidine. The specific genes that were searched are identified in Section 2.1 below.
The ability of psychotropic drugs to affect gene mRNA expression has the potential to modify the course of PD with either deleterious or therapeutic potential. Though it has been argued that genes correlate weakly with PD, the risk genes considered here are nonetheless significantly associated with PD, and have been demonstrated to affect PD risk at a statistical level, even if not well understood in terms of their biological significance. On the other hand, although some of the mutations and genes of interest have not yet demonstrated statistically significant relations to PD risk, they remain nonetheless of interest because of their putative pathobiological significance, and so they are also considered here. Thus, the genes considered in this report are either of statistical or biological significance in PD. Therefore, the effects of psychotropics, commonly used in treating patients with PD, on the transcription of these genes are of potential clinical interest and prompted this study.

2.0 Methods

2.1 Genes And Drugs Search Approach

The author comprehensively surveyed gene expression as a function of psychotropic treatment for genes associated with PD including classical mutation genes, risk-associated genes, and genes of interest by assessing literature in the PubMed database and data in the Gene Expression Omnibus Profiles database, last accessed on February 1, 2012. Search terms for drugs in these two databases were the drug categories and specific drugs detailed in Introduction Section 1.0.
paragraph 3, drugs chosen because they represent common first–line treatments in the United
States of America, and specific genes searched in these databases immediately follow.

*Classical mutation genes* included PARK1-16 mutations associated with PD (Gasser, 2009).

Specifically, these are: Parkinson disease, familial 1 (PARK1), parkinson protein 2, E3 ubiquitin
ligase (parkin) (PARK2), Parkinson disease 3 (autosomal dominant, Lewy body) (PARK3),
Parkinson disease (autosomal dominant, Lewy body) 4 (PARK4), ubiquitin carboxyl-terminal
esterase L1 (PARK5), Parkinson disease (autosomal recessive) 6 (PARK6), parkinson protein 7
(PARK7), Parkinson disease (autosomal dominant) 8 (PARK8), Parkinson disease (autosomal
recessive) 9 (PARK9), Parkinson disease 10 (susceptibility) (PARK10), Parkinson disease
(autosomal recessive, early onset) 11 (PARK11), Parkinson disease 12 (susceptibility) (PARK12),
HtrA serine peptidase 2 (PARK13), phospholipase A2, group VI (cytosolic, calcium-independent)
(PARK14), F-box protein 7 (PARK15), and Parkinson disease 16 (susceptibility
(PARK16).

*Risk-associated genes* consisted of those most strongly associated with PD according to the
PDGene database (Lill et al., 2012 <http://www.pdgene.org/>): microtubule-associated protein
tau / saitohin (MAPT/STH), synuclein, alpha (SNCA), acid beta-glucosidase (GBA), leucine-rich
repeat kinase 2 (LRRK2), peptidase M20 domain containing 1 (PM20D1), cyclin G associated
kinase (GAK), methylcrotonoyl-coenzyme A carboxylase I (MCCC1), lysosomal-associated
membrane protein 3 (LAMP3), serine threonine kinase 39 (STK39), bone marrow stromal cell
antigen 1 (BST1), glycoprotein (transmembrane) nmb (GPNMB), SET domain containing 1A
(SETD1A), genome-wide association at 8p22 (GWA_8p22), synaptotagmin XI / member RAS
oncogene family (SYT11/RAB25), family with sequence similarity 47, member E (FAM47E),
major histocompatibility complex, class II, DR beta 5 (HLA-DRB5), coiled-coil domain
containing 62 / huntingtin interacting protein 1 related (CCDC62/HIP1R),
aminocarboxymuconate semialdehyde decarboxylase / transmembrane protein 163
(ACMSD/TMEM163), and mediator complex subunit 13 (MED13). These risk – associated
genes generally exceed a level of 10⁻⁸ significance, range as high as 10⁻⁵², and their risk –
associated odds ratios are provided in Table 1. Descriptions of specific ethnic samples are
available on the PDGene website (Lill et al., 2012). Sample sizes used in the meta-analyses that
define the relationship of these genes to PD risk range from 677 to 53,380 subjects, with a mean
of 17,258.

**Genes of interest** were selected because they have at various points been associated with PD risk
in the PDGene database (Lill et al., 2012) or have emerged in recent meta-analyses of genome-
wide association studies (International Parkinson Disease Genomics Consortium et al., 2011) and
include nuclear casein kinase and cyclin-dependent kinase substrate 1 (NUCKS1), solute carrier
family 41, member 1 (SLC41A1), solute carrier family 45, member 3 (SLC45A3), pleckstrin
homology domain containing, family M (with RUN domain) member 1 (PLEKHM1),
diacylglycerol kinase, theta 110kDa (DGKQ), ubiquitin specific peptidase 24 (USP24),
GWA_12q23.3, superoxide dismutase 2, mitochondrial (SOD2), brain-derived neurotrophic
factor (BDNF), pyridoxal (pyridoxine, vitamin B6) kinase (PDXK), GWA 7p14.2,
apolipoprotein E (APOE), dopamine receptor D3 (DRD3), methylenetetrahydrofolate reductase
(NAD(P)H) (MTHFR), GWA 2q36.3, glutathione S-transferase mu 1 (GSTM1), major
histocompatibility complex, class II, DR alpha (HLA-DRA), PTEN induced putative kinase 1
(PINK1), fibroblast growth factor 20 (FGF20), solute carrier family 6 (neurotransmitter
transporter, dopamine), member 3 (SLC6A3), cytochrome P450, family 2, subfamily D,
polypeptide 6 (CYP2D6), GLIS family zinc finger 1 (GLIS1), monoamine oxidase B (MAOB),
28kDa calbindin 1 (CALB1), FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1
(chondrocyte-derived) (FARP1), low-density lipoprotein receptor-related protein 8 (LRP8), and
dopamine receptor D2 (DRD2). Additionally, Liu et al. (2011) recently identified genes with
genome wide significance in the range of $p<10^{-5}$ specifically within the Ashkenazi Jewish
population: solute carrier family 25, member 48 (SLC25A48), unc-13 homolog B (UNC13B),
solute carrier organic anion transporter family member 3A1 (SLCO3A1), wingless-type MMTV
integration site family, member 3 (WNT3), and N-ethylmaleimide-sensitive factor (NSF). 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
psychopharmacological category and specific names in each database. Only reports of chronic
administration (at least 3 weeks duration in animal studies) are considered here. (Studies of
prenatal exposure, primarily involving anticonvulsants, are not considered.)

2.2 Analysis Of GEO Profiles Data
Gene expression data in GEO Profiles were considered if a given treatment was compared to untreated controls under the same experimental conditions and if the data involved at least 2 determinations at a single locus. Gene expression data was found for the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine (mouse hippocampus by Affymetrix GeneChip® Mouse Genome 430 2.0 Array after 21 day treatment (GEO Profiles accession number GDS2803) (Miller et al., 2008)), the neuroleptic antipsychotic haloperidol and atypical antipsychotic clozapine (mouse whole brain by Affymetrix Gene Chip® Murine Genome U74 Version 2 Array [MG_U74Av2] after 4 week treatment (GDS2537) and by Affymetrix GeneChip® Mouse Expression 430A Array [MOE430A] after 12 week treatment (GDS2531)), and the atypical antipsychotics olanzapine (rat hippocampus by Affymetrix Gene Chip® Rat Genome 230 2.0 Array after 21 day treatment (GDS2608) (Fatemi et al., 2006)) and clozapine (as for haloperidol). GEO Profiles data were analyzed by a one-way ANOVA with Bonferroni correction.

Probe sets in GEO Profiles allow quantification of upregulation or downregulation of a given gene. Reporting of findings is limited to genes where specific probe sets of these genes were upregulated or downregulated by at least 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 (i.e., greater than a 20% change from untreated control values), probe sets were assessed and compared with each other to determine their reliability in assaying gene expression. Results are provided for genes for which changes in expression were observed after determining that the probe set showing a change was in fact a reliable probe of the gene’s transcription.
Normalized expression data in GEO Profiles were derived from a gene chip and remain to be confirmed by quantitative real time polymerized chain reaction (RT-PCR) or other analyses.

3.0 Results

3.1 General Findings

Relevant results in PubMed were found for PARK2 (PRKN, parkin), PARK5 (UCHL1), BDNF, DRD3, MAOB, LRP8, and DRD2. PubMed revealed no relevant gene expression data for most of the classical mutation genes (PARK 1/PARK4 (SNCA), PARK3, or PARK6-16), a number of risk associated genes (MAPT/STH, GBA, LRRK2, PM20D1, GAK, MCCC1/LAMP3, BST1, GPNMB, SETD1A, GWA_8p22, SYT11/RAB25, FAM47E, HLA-DRB5, CCDC62/HP1R, ACMSD/TMEM163, or MED13), or for many of the genes of interest including (NUCKS1, SLC41A1, SLC45A3, PLEKH1M1, DGKQ USP24, GWA_12q23.3, SOD2, PDXK, GWA 7p14.2, APOE, MTHFR, GWA 2q36.3, GSTM1, HLA-DR2, PINK1, FGF20, SLC6A3, CYP2D6, GLIS1, CALB1, FARP1, SLC25A48, UNC13B, SLCO3A1, WNT3, or NSF).

Relevant results in GEO Profiles were found for PARK2 (PRKN, parkin), PARK5 (UCHL1), MAPT, GBA, MCCC1, SETD1A, CCDC62, HIP1R, TMEM163, BDNF, GSTM1, and CALB1, SLCO3A1, and UNC13B. GEO Profiles revealed no gene expression data for PARK 3, PARK10-12, PARK 14-16, HLA-DRB5, GWA_12q23.3, MTHFR, GWA 7p14.2, GWA2q36.3, HLA-DRA, or SLC25A48. Although expression data were available in GEO Profiles, data analysis demonstrated no appreciable effects by fluoxetine, haloperidol, olanzapine, or clozapine on the classical mutation genes PARK1/PARK4 (SNCA), PARK6-9, and PARK13, risk
associated genes SNCA, LRRK2, PM20D1, GAK, LAMP3, STK39, BST1, GPNMB, SYT11, RAB25, ACMSD, and MED13, or genes of interest NUCKS1, SLC41A1, SLC45A3, PLEKHM1, DGKQ, USP24, SOD2, PDXK, APOE, DRD3, FGF20, SLC6A3, CYP2D6, GLIS1, MAOB, FARP1, LRP8, DRD2, WNT3, or NSF, although there were no data for fluoxetine for ACMSD or TMEM163, 4-week haloperidol or clozapine for GAK, LAMP3, 4- and 12-week haloperidol or clozapine for CCDC62, ACMSD, MED13, MAOB or PLEKHM1, or for olanzapine or 4-week haloperidol and clozapine for FARP1, LRP8, GPNMB, or DGKQ, or for olanzapine alone for SETD1A or WNT3. Olanzapine data were compromised by lack of detection call (a measure of reliability) for MCCC1, LAMP3, SYT11, RAB25, HIP1R, ACMSD, TMEM163, PDKX, DRD3, SLC6A3, GPNMB, and DRD2. The antipsychotics (olanzapine, haloperidol, clozapine) did not appreciably affect PARK5 (UCHL1), MAPT, GBA, or BDNF, and neither haloperidol nor clozapine appreciably affected GSTM1.

Positive findings (i.e., changes of at least 20% in mRNA expression) in GEO Profiles were thus restricted to TMEM163, GSTM1, and SLCO3A1 for olanzapine, and PARK2 (PRKN, parkin), PARK5 (UCHL1), MAPT, GBA, MCCC1, SETD1A, CCDC62, HIP1R, BDNF, GSTM1, CALB1, and UNC13B, and SLCO3A1 for fluoxetine. Only positive findings from the literature and GEO Profiles searches are summarized below.

3.2 Classical Mutations

PARK2 (PRKN, parkin, 6q25.2-q27). Mutations are associated with sporadic PD and with recessive early onset, slowly progressive, parkinsonism lacking Lewy bodies. Four weeks of haloperidol induced striatal mRNA in rat striatum (Nakahara et al., 2001) in contrast to rat...
whole-brain negative findings (i.e., <20% change) in GEO Profiles, suggesting upregulation specific to the nigrostriatal system.

**PARK5** (UCHL1, 4p14). Mutations are linked to autosomal dominant, levodopa - responsive PD with onset in the 6th decade. Chronic antipsychotic treatment in schizophrenia downregulated UCHL1 mRNA in the prefrontal cortex relative to matched healthy controls and drug-naïve patients (Vawter et al., 2001). In GEO Profiles, fluoxetine upregulated PARK5 expression by a factor of 1.33 (i.e., 33% upregulation) at probe set ID 1448260_at (NCBI reporter NM_011670), the only probe set used in the investigation.

### 3.3 Risk Associated Genes

**MAPT** (microtubule-associated protein tau, 17q21.1). Increased promoter region function, especially with the H1 haplotype, is associated with late-onset PD. In GEO Profiles, fluoxetine downregulated Mapt by a factor of 0.75 (i.e., 25% downregulation) at 1455028_at (BQ178510), the probe set with the greatest identity (97.54), although less so (0.81, 0.85, 0.88) at less specific probe sets.

**GBA** (acid beta-glucosidase, 1q21). GBA mutations are linked to PD. In GEO Profiles, fluoxetine upregulated Gba expression at both probe sets studied, by a factor of 1.30 at 1450099_a_at (NM_008094) and 1.36 at 1437044_a_at (BB241507).

**MCCC1** (methylcrotonoyl-coenzyme A carboxylase I (alpha), 3q27). PD risk has been mapped to an intergenic single nucleotide polymorphism (SNP) in this area. In GEO Profiles, fluoxetine
downregulated Mccl1 expression at both probe sets studied, by a factor of 0.79 at 1417227_at (NM_023644) and 0.78 at 1458208_s_at (BB770903).

**SETD1A** (SET domain – containing protein 1A, 16p11.2). SETD1A is a histone 3 lysine 4 methyltransferase that methylates H3 histones to activate transcription and is linked to PD. In GEO Profiles, although fluoxetine downregulated Setd1a expression at 1450336_at (NM_010940), this probe set was far less well annotated and had a poorer identity (36.98) than 1427116_at (C87155; identity 94.68), which showed only a 10% downregulation.

**CCDC62/HIP1R** (coiled-coil domain containing 62, 12q24.31; huntingtin interacting protein 1 related, 12q24). PD risk has been linked to an intronic SNP in CCDC62. In GEO Profiles, fluoxetine upregulated Ccdc62 at AI661708 by 1458644_at (1.23), the only probe set studied. Fluoxetine also upregulated Hip1r by a factor of 1.21 at AA590970 by 1425551_at, but not at two other probe sets of the same reporter (1458208_s_at (0.98) and 1425553_s_at (1.01)). All three Hip1r probe sets had identities of 98.64 and coverages of 98.6, and each lacked cross-hybridizing transcripts.

**TMEM163** (transmembrane protein 163, 2q21.3). An intronic TMEM163 SNP is linked to PD risk. In GEO Profiles, olanzapine upregulated Tmem163 by a factor of 1.28 at BI293607 by 1382222_at. The only other probe set data (AW251322 by 1375398_at) was compromised by lack of detection call in all cells.
3.4. Genes Of Interest

**BDNF** (brain-derived neurotrophic factor, 11p13). A rare functional G196A (Val66Met) BDNF variant is associated with early onset PD. Among antipsychotic medications, the rat literature reveals hippocampal and cortical Bdnf mRNA downregulation with haloperidol (Bai et al., 2003; Lipska et al., 2001; Park et al., 2009) (one study showed no change (Keilhoff et al., 2010)), both upregulation (Bai et al., 2003) and downregulation (Lipska et al., 2001) with clozapine (10mg/kg for 28 days (Bai et al., 2003; Lipska et al., 2001)), upregulation with olanzapine (Bai et al., 2003), quetiapine (Park et al., 2006), and lurasidone (Fumagalli et al., 2011), and no effect with risperidone (Keilhoff et al., 2010) or ziprasidone (Park et al., 2009). Chronic paliperidone upregulated Bdnf mRNA in rat hippocampal CA1/2, CA3, and dentate gyrus in rats (Hanson et al., 2011). In primate prefrontal cortex however, neither long-term treatment with haloperidol in monkeys (Hashimoto et al., 2005) nor chronic antipsychotic treatment in schizophrenia affected BDNF mRNA expression (Wong et al., 2010).

The mood stabilizer lithium downregulated hippocampal Bdnf mRNA expression in adult rats (Hanson et al., 2011; Jacobsen et al., 2004) and in ovariectomized mice (Valdes et al., 2010), but upregulated it in the cortex of these mice (Valdes et al., 2010). Chronic treatment with the mood stabilizing anticonvulsant carbamazepine upregulated BDNF mRNA expression in rat frontal cortex (Chang et al., 2009).

In rats treated for 21 days, the antidepressants imipramine (Larsen et al., 2008; Rogóz et al., 2007), sertraline (Nibuya et al., 1995), paroxetine (Martínez-Turrillas et al., 2005), venlafaxine (Larsen et al., 2008), and duloxetine (Calabrese et al., 2007; Molteni et al., 2009) each
upregulated BDNF mRNA expression. Among tricyclic antidepressants (TCAs), chronic
imipramine treatment upregulated hippocampal dentate gyrus Bdnf above the elevation in
dentate and CA3 area associated with the chronic unpredictable stress rat model of depression
(Larsen et al., 2010). Desipramine given for 21 days upregulated Bdnf in rat hippocampus
(Dwivedi et al., 2006; Jacobsen et al., 2004; Li et al., 2000; Nibuya et al., 1995) and frontal
cortex (Dwivedi et al., 2006) but, in two studies, downregulated hippocampal mRNA
(Torregrossa et al., 2005) and had no effect on cortex (Jacobsen et al., 2004; Torregrossa et al.,
2005). Neither chronic amitriptyline in mice undergoing spinal nerve transection (Hu et al.,
2010) nor chronic nortriptyline in Sprague Dawley rats (Hansson et al., 2011) increased
hippocampal Bdnf mRNA above control levels.

Among selective serotonin reuptake inhibitors (SSRIs), fluoxetine administered for 21 days
upregulated Bdnf mRNA in rat hippocampus (Dwivedi et al., 2006; Molteni et al., 2006;
Musazzi et al., 2009) (but without effect in two studies (Hanson et al., 2011; Torregrossa et al.,
2005)), visual cortex (Vetencourt et al., 2011), and in ventral tegmental area and nucleus
accumbens shell although this was not evident in substantia nigra or striatum (Molteni et al.,
2006). Chronic fluoxetine administration increased hippocampal BDNF mRNA expression in
C57BL/6 mice but not in BALB/c mice (Farley et al., 2012). Increased expression in visual
cortex was linked to reduced expression of the histone deacetylase Hdac5 and increased histone
acetylation of the promoter region of the Bdnf gene (Vetencourt et al., 2011). In adult male
Wistar rats, 8 weeks of fluoxetine treatment did not, however, alter brainstem BDNF gene
expression (Shishkina et al., 2012). In the glucocorticoid receptor impaired transgenic mouse
model of affective disorder, chronic treatment with fluoxetine reversed the model’s hippocampal
Bdnf mRNA downregulation (Païzanis et al., 2010). The SSRI fluvoxamine administered for 6 weeks to augment antipsychotic treatment in schizophrenic patients with prominent negative symptoms upregulated peripheral mononuclear cell BDNF that increased over the treatment course (Silver et al., 2011). Although chronic escitalopram did not affect hippocampal Bdnf expression in rats (Hansson et al., 2011; Jacobsen et al., 2004), 12 week treatment increased leukocyte BDNF mRNA expression, correlating with serum BDNF level and symptomatic improvement, in patients with depression (Cattaneo et al., 2010).

The norepinephrine-dopamine reuptake inhibiting antidepressant bupropion downregulated hippocampal Bdnf mRNA expression when chronically administered to Sprague Dawley rats (Torregrossa et al., 2005). The serotonin – norepinephrine reuptake inhibitor (SNRI) venlafaxine upregulated hippocampal dentate gyrus Bdnf mRNA above control levels in rats subjected to chronic unpredictable stress as a model of depression (Larsen et al., 2010), although venlafaxine was not found to change Bdnf mRNA expression in rats under more conventional conditions (Calabrese et al., 2011). The SNRI duloxetine upregulated reduced BDNF coding exon IX mRNA expression in the hippocampus and prefrontal cortex after chronic administration in a serotonin transporter knockout rat model of depression, although this did not correlate with BDNF protein levels in frontal cortex (Calabrese et al., 2010).

An antidepressant with melatonin MT1 and MT2 receptor agonist and 5HT2 receptor antagonist properties, agomelatine, has upregulated hippocampal in rats (Calabrese et al., 2011) and in the glucocorticoid receptor impaired mouse model of affective disorder (Païzanis et al., 2010), but not in prefrontal cortical Bdnf in rats (Calabrese et al., 2011). In patients with schizophrenia that
had been treated with antidepressants, BDNF mRNA expression in dorsolateral prefrontal cortex, parietal cortex, and hippocampus was upregulated, in contrast to schizophrenic untreated controls (Wong et al., 2010).

In GEO Profiles, chronic fluoxetine upregulated Bdnf expression robustly at the only two probe sets studied, by a factor of 5.04 at 1422169_a_at (AY057913) and 4.45 at 1422168_a_at (AY057913).

**DRD3** (dopamine receptor D3, 3q13.3). It is not entirely clear how DRD3 affects PD risk although DRD3 mRNA is reduced in PD lymphocytes, unrelated to treatment. Although haloperidol for 21 days did not affect rat lymphocyte Drd3 mRNA expression (Caronti et al., 1999), rat brain studies demonstrate that chronic haloperidol (Buckland et al., 1992; D'Souza et al., 1997), loxapine (Buckland et al., 1992; D'Souza et al., 1997), clozapine (D'Souza et al., 1997), and pimozide (D'Souza et al., 1997), each upregulated whole brain D3 mRNA after 32 days. In human lymphocytes as in rat lymphocytes, antipsychotic treatment did not affect DRD3 expression in patients with schizophrenia or bipolar disorder (Ilani et al., 2001; Vogel et al., 2004). After chronic administration of at least 21 days, amitriptyline, desipramine, imipramine, fluoxetine, tranylcypromine, and electroconvulsive therapy each upregulated D3 mRNA expression in the nucleus accumbens shell (Lammers et al., 2000).

**GSTM1** (glutathione S-transferase mu 1, 1p13.3). The GSTM1 null genotype is linked to PD in the contexts of CYP2D6 poor metabolizer status and solvent exposure. In GEO Profiles, fluoxetine downregulated Gstm1 expression by a factor of 0.77 at 1448330_at (NM_010358) and
0.82 at 1416416_x_at (NM_010358), but not at probe sets with significantly lesser identities (0.99 at 1425626_at and 0.92 at 1425627_x_at). Olanzapine upregulated Gstm1 expression by a factor of 1.20 at 1386985_at (M28241), the only probe set studied.

**MAOB** (monoamine oxidase B, Xp11.23). The MAOB G genotype is variably associated with PD risk, especially in men. Risperidone (Chen et al., 2005, 2007) and olanzapine (Chen et al., 2007) (but not haloperidol or clozapine (Chen et al., 2007)) treatment for 4 weeks in rats upregulated frontal cortical Maob expression.

**CALB1** (28kDa calbindin 1, 8q21.3-q22.1). The CALB1 SNP rs1805874 is linked to PD risk. In GEO Profiles, chronic fluoxetine downregulated Calb1 expression at all probe sets studied, by a factor of 0.73 at 1417504_at (BB246032), 0.45 at 1448738_at (BB246032), 0.50 at 1456934_at (BB177770), and 0.66 at 1458836_at (AW557885), with 1417504_at being the best supported with an identity of 95.56.

**LRP8** (low-density lipoprotein receptor-related protein 8, 1p34). LRP8 knockout increases tau phosphorylation in mice, suggesting a relation to MAPT. Antipsychotic administration downregulated ApoER2 (LRP8) mRNA in peripheral lymphocytes after 6 months of treatment compared to pre-treatment baseline in drug-naïve patients with schizophrenia (Suzuki et al., 2008).

**DRD2** (dopamine receptor D2, 11q23). Knockout in mice produces parkinsonism, and the TaqIa polymorphism, especially the A1A1 genotype, and 15-allele polymorphism are linked to PD
motor fluctuation risk. DRD2 deficient mice manifest akinesia and bradykinesia resembling PD. In post-mortem brains of patients with schizophrenia (treated with antipsychotics), some dying of suicide, frontal cortical DRD2 mRNA was similar to normal controls (Urigüen et al., 2009) and untreated schizophrenia (Tallerico et al., 2001). Although several early studies did not find murine striatal D2 mRNA expression changes after chronic haloperidol treatment (Matsunaga et al. 1991; Srivastava et al., 1990; van Tol et al., 1990), subsequent studies found upregulation (Bernard et al., 1991; Buckland et al., 1992, 1993; Fishburn et al., 1994; Jaber et al., 1994; Rogue et al., 1991). In rats, 32-day treatment with antipsychotics dose-dependently upregulated D2 mRNA expression in the striatum (haloperidol), prefrontal cortex (haloperidol), and whole brain (loxapine) (Buckland et al., 1993; D'Souza et al., 1997). In rat pituitary, 21 days of haloperidol upregulated, aripiprazole downregulated, and clozapine did not affect D2 mRNA expression (Inoue et al., 1998). In the ventral tegmental area, both aripiprazole and olanzapine increased D2 mRNA expression after 12 weeks of treatment (Han et al., 2009). Six-months treatment with chlorpromazine, haloperidol, molindone, pimozide, risperidone, olanzapine, and clozapine upregulated prefrontal and temporal cortical D2 mRNA expression in primates, but in contrast to the other drugs, clozapine and olanzapine did not affect striatal DRD2 expression (Lidow et al., 1997). Chronic lithium treatment and lithium withdrawal did not affect D2 mRNA expression in the ventral tegmental area (Ferrie et al., 2008). Chronic treatment with amitriptyline and/or imipramine, but not desipramine, fluoxetine, tranylcypromine, or electroconvulsive treatment, each increased D2 mRNA expression in rat striatum (Lammers et al., 2000). Thus, antipsychotics and tertiary amine tricyclic antidepressants upregulate Drd2 mRNA in at least one brain site, with haloperidol, other neuroleptics, and certain tricyclics upregulating striatal Drd2 mRNA.
**UNC13B** (unc-13 homolog B (C. elegans), 9p13.3). The protein product is involved in priming synaptic vesicular exocytosis via syntaxin, and in regulating neurotransmission (Liu et al. 2011). Renal cells transfected with this gene and exposed to hyperglycemic—induced increases in diacylglycerol undergo apoptosis. In GEO Profiles, fluoxetine upregulated Unc138 by a factor of 1.39 at NM_021468 by 1417757_at (identity 97.57) but only 1.03 at AV231882 by 1443308_at (identity 81.58).

**SLCO3A1** (solute carrier organic anion transporter family, member 3A1, 15q26). The protein product of this gene is enriched in brain glia and neurons, especially in frontal cortical neuronal gray and white matter axons and soma, and has mediated the transport of estrone-3-sulfate, prostaglandins E1 and E2, thyroxine, and vasopressin. It is likely associated with neuronal signaling associated with reuptake mechanisms. In GEO Profiles, olanzapine upregulated Slco3a1 by a factor of 1.47 at AI101171 by 1373734_at, the only of 2 reporter data sets that had data cells not compromised by absent detection calls. Nonetheless, even for this probeset, 2 of 4 data cells had absent detection calls, indicating a need for confirmation.

### 4.0 Discussion

These findings indicate that psychotropic drugs commonly prescribed in PD can affect the transcription of genes associated with the risk of developing PD when administered chronically in animals and humans for at least 21 days, summarized by gene in Table 1 and by drug in the
abstract. Fluoxetine effects on BDNF and UCHL1 in GEO Profiles remained significant after
Bonferroni correction (Table 2), 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 PD management upon more specific analyses of the nigrostriatal system with more
sensitive and reliable real time polymerized chain reaction (RT-PCR) using reverse transcription.

It must be emphasized that these data are reflective of an early and nascent heterogeneous
literature involving uneven and unsystematic study of both genes and drugs. It is therefore
premature to rely upon statistical analyses of these findings. Nevertheless, the statistical results
are provided at this point only as an initial consideration for those who may be interested. It is
important to recognize that this is an evolving dynamic literature, with the strength of gene
associations fluctuating depending on the influence of forthcoming data.

Many of the genes mentioned here have not been well – studied, especially some of the newer
more highly associated risk genes, and their relation to PD pathobiology is even still more
cryptic at this point. Though it has been argued that genes correlate weakly with PD, the risk
genes considered here are nonetheless significantly associated with PD, and have been
demonstrated to affect PD risk at a statistical level, even if not well understood in terms of their
biological significance. Thus, although the pathobiological relationship to PD of many of the
risk genes is yet emerging, they are considered here because of their statistical relationship. In
contrast, mutations and genes of interest are considered because of their putative biological
relationship to PD and not because of their statistical properties.
Clearly, PD–associated genes are not the only genes affected by psychotropics, and transcriptional explorations in GEO Profiles of leading genes associated with type II diabetes mellitus and antipsychotic–induced diabetes and weight gain (TCF7L2, PPARγ, KCNJ11, IGF2BP2, HHEX, CDKAL1, SLC30A8, FTO, CNR1) revealed that IGF2BP2 exceeded the 20% threshold and was upregulated by a factor of 1.31 (Lim et al. 2010; Irvin et al. 2009; Tiwari et al. 2010; Tiwari et al. 2011; Vehof et al. 2011). This is comparable to the transcriptional changes observed in the present study, instilling confidence that PD gene expression induced by psychotropics can potentially affect PD onset and progression in a clinically meaningful manner. To provide an index of comparability for the psychotropic–related transcription findings for PD–related genes to other types of genes, the effects of olanzapine and clozapine were evaluated on the expression of genes associated with antipsychotic–induced weight gain and diabetes, and other diabetes mellitus genes using GEO Profiles data. These drugs and genes were chosen because these drugs are notorious for their association with induction of weight gain and diabetes. Genes associated with antipsychotic–induced weight gain include cannabinoid receptor 1 (CNR1) (Tiwari et al. 2010), potassium channel inwardly rectifying subfamily J member 11 (KCNJ11) (Tiwari et al. 2011), solute carrier family 30 member 8 (SLC30A8) (Tiwari et al. 2011), fat mass and obesity–associated (FTO) (Tiwari et al. 2011), and the H1 histamine receptor (HRH1) (Vehof et al. 2011). Antipsychotic–induced diabetes is associated with transcription factor 7–like 2 (T cell–specific, HMG box) (TCF7L2) (Irvin et al. 2009). Independent of antipsychotics, genes most frequently associated with Type II diabetes mellitus include...
TCF7L2, peroxisome proliferators-activated receptor gamma (PPARG), KCNJ11, insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2), hematopoietically-expressed homeobox (HHEX), CDK regulatory subunit associated protein 1-like 1 (CDKAL1), SLC30A8, and FTO according to the Type 2 Diabetes Genetic Association Database (Lim et al. 2010 <http://t2db.khu.ac.kr:8080/>). Antipsychotic-induced gene transcription changes in GEO Profiles were usually less than 4%, with only a few as high as 8-9%, and olanzapine, the antipsychotic most notoriously associated with diabetes, downregulating CNR1 by 15% but upregulating IGF2BP2 transcription 31% (by a factor of 1.31, reporter AI058451 by probeset 1382609_at). The overall change in transcription of PD and dysmetabolic genes was comparable, and for the noteworthy transcription changes reported in the Results section, of the same magnitude as for IGF2BP2. This instills confidence that the level of change in PD gene expression induced by psychotropics may have the potential to translate into clinically relevant effects on PD course since antipsychotic-induced weight gain and diabetes themselves are clinically apparent phenomena.

Functional analyses (haplotype, mutation severity, null alleles, and knock-out models) of MAPT, GBA, BDNF, and DRD2 indicate that fluoxetine, imipramine, certain other serotonergic antidepressants, atypical antipsychotics, and neuroleptics may attenuate PD risk whereas lithium and bupropion may augment PD risk (although these effects may differ in patients with specific mutations or variants such as the GBA mutation and G196A BDNF variant). The biological role of these genes (Figures 1 and 2) is currently incompletely understood and BDNF may relate more to neuroregeneration than to PD risk.
Most research to date has focused on cortical and hippocampal regions in this early literature, and the striatum and substantia nigra remain to be investigated. It should be kept in mind, however, that PD-associated genes themselves need not necessarily be affected within nigrostriatal tracts in order to exert their influence on PD risk because their risk may be mediated through interactions with other factors or genes yet to be discovered. There remains, however, a need to confirm these drug effects in research paradigms that are more clinically relevant to PD, described below.

It can nevertheless be said at this point that specific psychotropics may meaningfully alter the transcription of genes that are important to developing PD (inferred from the association of gene mutations and variants with PD risk). It is possible that transcriptional effects on these genes may affect PD risk and clinical progression, although this remains to be demonstrated since transcription may not correlate with protein concentration (e.g., lithium downregulates BDNF gene expression but increases BDNF (Jacobsen et al., 2004)).

Limitations of this investigation include problems inherent to an uneven, unsystematic, and emerging literature, and the limitations inherent to literature searches. Additionally, gene definitions, risk rankings, probe sets, gene functions, gene roles in PD, and expression data are evolving, meaning that the relevance of some of the current findings may become obsolete over time. The study of heterogeneous species, cross-species translational validity between rodents and humans, varying degrees of gene association in different PD populations and with Lewy body histopathology, and potentially differential gene or drug effects in different populations or
at different PD stages provide the possibility that some of the findings summarized here may not apply in human PD or may be relevant only in certain PD subpopulations. Furthermore, reliance on a single technology in the GEO Profiles data (i.e., Affymetrix gene chips), multiple gene effects of a single drug that may vary in potency and by drug dose, gene – gene interactions, epigenetic interactions, and sometimes – conflicting findings in the literature may also impede the translation of these findings into clinically important effects. For example, although PRKN (PARK2) mutations are classically associated with parkinsonism lacking Lewy bodies, they can also be associated with Lewy body – positive parkinsonism (Farrer et al., 2001). Also, PARK5 UCHL1 S18Y mutations have been pathogenic, protective, or without effect, depending upon the specific study (Maraganore et al., 2004). Although the classical mutations and genes of interest generally have low attributable risk for PD in contrast to the risk associated genes, and may or may not be causally linked to PD pathobiology, they are nevertheless empirically associated with PD risk and represent the best genetic correlates available to date. Furthermore, each risk gene variant has been replicated (except for PRKN) in a large number of subjects (except for GBA), with odds ratios ranging between 0.75 – 0.93 and 1.08 - 3.27. It remains possible that medicines or other simultaneously expressed genes mask their apparent attributable risk for PD through epigenetic or gene – gene interactions, and that causal relevance will be forthcoming as PD pathobiology is further elucidated, increasing their relevance to PD risk and progression.

The current absence of established risk - modifying treatments, the frequency with which psychotropic drugs are used, and these initial promising findings prompt the need for further study of psychotropics on these genes that have already been established to confer risk in PD.
Ideally, future study will include determinations of: (1) nigrostriatal gene expression in animals undergoing treatment with these drugs for at least 3 months; (2) the relative risk for PD in patients chronically treated with these drugs; (3) relative correlations of nigrostriatal transcription of target genes with transcription in other more readily – accessible proxy sites, such as peripheral monocytes, cerebrospinal fluid, etc.; (4) gene transcription at well – correlated proxy sites by RT-PCR in PD patients chronically treated with these agents at a stable dose for at least 3 months; and (5) study of other PD risk genes using these approaches, since extant data have not involved these methods and have, therefore, not excluded potential drug effects on these genes. These approaches may help reduce confounds including cross – species translation, gene chip technology, and site – specific, time – dependent, and dose – related transcription effects. Effects of these drugs on the specific mutations and polymorphisms associated with PD risk are less clear and are likely to remain so until data sets of sufficient size can be analyzed.

There are of course many other effects of psychotropics that can impact multiple processes at the neuronal level (Lauterbach et al., 2010a,b; Lauterbach and Mendez, 2011), and gene expression is only one of many of these processes that can influence neurodegenerative outcome. Whether transcriptional effects will play an important role in neuroprotection remains to be determined. In any event, this report provides an initial framework to consider the potential impact of commonly prescribed drugs on genes that are relevant to PD. The effects of psychotropics on the expression of these genes should now be studied further as outlined above.

Conclusion
Psychotropics are widely prescribed for neuropsychiatric disorders in PD and affect a diverse array of genes, some of which are implicated PD pathobiology. The results of the present study indicate that first-line psychotropics used in managing patients with PD affect the transcription of genes that have been statistically and biologically linked to PD pathogenesis. Several antipsychotics and serotoninergic drugs show potential to serve as neuroprotectants, while lithium and bupropion may foster progression, based on preliminary transcriptional effects of MAPT, GBA, CCDC62, HIP1R, DBDNF, and DRD2, although multiple limitations apply to these findings. Clinical studies of these drugs on these genes and on PD progression are now needed.

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Captions For Figures

Figure 1. **Intraneuronal Neurodegenerative Pathways.** Interactions of genes with Parkinson’s disease neuroprotective and neurodegenerative pathways. Relations terminating in an arrowhead indicate facilitation, those with double arrowheads indicate mutual facilitation, whereas dashed lines with bulbous terminations indicate inhibition. αSyn refers to alpha synuclein, tau to tau protein, and ROS to reactive oxygen species. Other terms refer to gene designations.

Figure 2. **Neuronal Viability Mechanisms.** Factors affecting the viability of nigrostriatal dopamine neurons and striatopallidal GABAergic neurons, leading to normal motor function and the absence of Parkinson’s disease manifestations. Relations terminating in an arrowhead indicate facilitation, and dashed lines terminating in a bulb indicate inhibition. αSyn refers to alpha synuclein, Aβ to beta-amyloid protein, tau to tau protein, and ROS to reactive oxygen species. Other terms refer to gene designations.
Supplementary Information For Figure 1

MAPT transcription produces tau protein, and LRP8 can negatively modulate MAPT activity.

PARK1/4 (SNCA) transcription produces alpha-synuclein (αSyn), which can facilitate tau formation. αSyn and tau mutually facilitate their aggregation. αSyn inhibits apoptosis whereas mono-ubiquitylated αSyn translocates to the neuronal nucleus and is associated with apoptosis. Aggregated proteins including αSyn and tau can ultimately produce mitochondrial dysfunction, reactive oxygen species (ROS), and apoptosis, and can inhibit the proteasome. These and other aggregated or obsolete proteins are ubiquitylated and degraded in the proteasome. PARK5 (UCHL1) transcription regulates the availability of ubiquitin monomers while PARK2 (parkin) ligates ubiquitin tags to these proteins to signal proteasomal processing. PARK2 also attenuates ROS-induced inflammation. GSTM1 and CYP2D6 gene products promote solvent detoxification, and deficiencies in these proteins permit toxicity. GSTM1 becomes particularly important in the context of CYP2D6 dysfunction. Toxins and mitochondrial dysfunction can predispose to or cause apoptosis. The MAOB gene encodes monoamine oxidase B (MAOB), which can generate ROS when oxidizing dopamine and other molecules. ROS can produce mitochondrial dysfunction and inflammation, and vice versa. Ubiquitylated αSyn, damaged and aggregated proteins, toxins, proteasomal dysfunction, mitochondrial dysfunction, and ROS can each induce apoptosis, thereby killing the cell, while αSyn itself can deter apoptosis.

Supplementary Information For Figure 2

Toxins, inflammation, aggregated proteins (including αSyn, Aß, and tau), apoptosis, reactive oxygen species (ROS), and mitochondrial dysfunction all lead to reduced cellular viability or death, including dopamine neurons. BDNF transcription produces the neurotrophin BDNF.
DRD3 transcription leads to dopamine D3 receptors, which have a role in regulating trophic support of substantia nigra neurons and their neurogenesis. The product of the HIP1R gene assists in maintaining neuronal presynaptic function while the effects of UNC13B and SLC03A1 are not yet clear. Although their mechanisms are currently cryptic, a variety of other genes (GBA, MCCC1, CCDC62, CALB1, ACMSD) also appear to support and protect nigrostriatal presynaptic neurons. DRD2 encodes the dopamine D2 receptor, borne on striatopallidal GABAergic neurons. The proper functioning of these striatal neurons is critical to normal motor function, and they are regulated by nigrostriatal dopamine acting on striatal D2 receptors. Striatal neurons are supported and maintained by BDNF, other trophic and neurogenic factors, and by the product of the TMEM163 gene, the mechanism for which awaits discovery. Loss of presynaptic nigrostriatal neuron dopamine release on striatal D2 receptors leads to the manifestations of Parkinson’s disease.
Psychotropic Drug Effects On Gene Transcriptomics Relevant To Parkinson’s Disease

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Abstract

Objectives: Psychotropic drugs are widely prescribed in Parkinson’s disease (PD) without regard to their pathobiological effects, and these drugs affect the transcription of a large number of genes. Effects of these drugs on PD risk gene transcription were therefore surveyed. Methods: Results summarize a comprehensive survey of psychotropic effects on messenger ribonucleic acid (mRNA) expression evident in published data for 70 genes linked to PD risk. Results: Psychotropic drugs can meaningfully affect PD risk gene mRNA transcription, including antipsychotics (upregulate dopamine receptors D2 and D3 (DRD2, DRD3); downregulate low-density lipoprotein receptor-related protein 8 (LRP8), ubiquitin carboxyl-terminal esterase L1 (UCHL1, also known as PARK5)), haloperidol (upregulates DRD3, parkin (PRKN, also known as PARK2), DRD2; downregulates brain-derived neurotrophic factor (BDNF)), risperidone (upregulates monoamine oxidase B (MAOB), DRD2), olanzapine (upregulates transmembrane protein 163 (TMEM163), BDNF, glutathione S-transferase mu 1 (GSTM1), MAOB, DRD2, solute carrier organic anion transporter family, member 3A1 (SLCO3A1)), aripiprazole (upregulates DRD2), quetiapine, paliperidone, lurasidone, carbamazepine, and many antidepressants (upregulate BDNF), lithium and bupropion (downregulate BDNF), amitriptyline (upregulates DRD3, DRD2), imipramine (upregulates BDNF, DRD3, DRD2), desipramine (upregulates BDNF, DRD3), and fluoxetine (upregulates acid beta-glucosidase (GBA), coiled-coil domain containing 62 (CCDC62), BDNF, DRD3, UCHL1, unc-13 homolog B (UNC13B), and perhaps huntingtin interacting protein 1 related (HIP1R); downregulates microtubule-associated protein tau (MAPT), methylcrotonoyl-coenzyme A carboxylase I (MCCC1), GSTM1, 28kDa calbindin 1 (CALB1)). Fluoxetine effects on BDNF and UCHL1 in GEO Profiles were statistically robust. Conclusions: This report provides an initial summary and framework to understand the potential impact of psychotropic drugs on PD-relevant genes. Antipsychotics and serotonergic antidepressants may potentially attenuate PD risk, and lithium and bupropion may
augment risk, through MAPT, GBA, CCDC62, HIP1R, BDNF, and DRD2 transcription, with MAPT, GBA, and CCDC62 being strongly associated with PD risk in recent meta-analyses.

Limitations of these findings and a research agenda to better relate them to the nigrostriatum and PD are discussed.

**Key Words:** Parkinson’s disease, antipsychotics, antidepressants, gene expression, mRNA, risk

1.0 Introduction

Neuropsychiatric conditions occur in more than half of patients with Parkinson’s disease (PD) and exact significant morbidity (Lauterbach, 2005, 2004). Among these conditions, psychotic, mood, and anxiety disorders figure prominently. Psychotic symptoms occur in up to 50%, manic symptoms in 10%, and both are treated with antipsychotics. Depressive and anxiety disorders each occur in at least 40% of PD patients, and both are treated with antidepressants.

Additionally, anxiety disorders and sleep disorders, which have been documented in up to 90% of patients with PD, are treated with anxiolytics and, at times, antihistaminic agents (Lauterbach, 2005, 2004). Thus, psychotropics are commonly used to treat these conditions although the effects of these drugs on PD pathobiology are not well known (Lauterbach et al., 2010b).

A large number of genes have been implicated in the risk and pathogenesis of PD, and ongoing meta-analyses are determining their statistical associations. Psychotropics can affect the expression of many genes and, therefore, potentially the expression of genes involved in PD. The author was interested in the effects of these drugs on the expression of genes associated with PD (specifically, mutations, risk genes, and genes of interest) and explored these effects in
National Library of Medicine published medical literature and gene expression databases. As
this is a relatively nascent and emerging literature, it was anticipated that there might be a
number of limitations to the data, but that some early clues might be gleaned that could inform
and direct future research efforts. The goal of this survey, then, was to examine the potential of
first – line psychotropics available in the United States, drugs that are frequently employed in the
management of PD, to influence the expression of genes catalogued in a PD risk gene database
that are either statistically or pathobiologically implicated in PD risk.

More specifically, these first line psychotropics involved the following drug categories and
specific drugs: neuroleptic, atypical antipsychotic, antipsychotic, antidepressant, tricyclic
antidepressant, heterocyclic antidepressant, selective serotonin reuptake inhibitor, SSRI,
anxiolytic, benzodiazepine, pramipexole, ropinirole, amantadine, haloperidol, fluphenazine,
trifluoperazine, thiothixene, chlorpromazine, thioridazine, risperidone, olanzapine, quetiapine,
ziprasidone, aripiprazole, clozapine, paliperidone, iloperidone, asenapine, lurasidone,
tetrabenazine, pimavanserin, lithium, carbamazepine, oxcarbazepine, valproate, lamotrigine,
amitriptyline, imipramine, nortriptyline, desipramine, clomipramine, trimipramine, doxepin,
protriptyline, maprotiline, bupropion, fluoxetine, sertraline, fluvoxamine, paroxetine, citalopram,
s-citalopram, trazodone, nefazodone, venlafaxine, duloxetine, mirtazapine, atomoxetine,
bupropion, diazepam, chlordiazepoxide, flurazepam, temazepam, chlorazepate, clonazepam,
lorazepam, oxazepam, alprazolam, zaleplon, zolpidem, zopiclone, s-zopiclone, cyproheptadine,
hydroxyzine, diphenhydramine, benztropine, trihexyphenidyl, modafinil, ramelteon,
dextromethorphan, and quinidine. The specific genes that were searched are identified in
Section 2.1 below.
The ability of psychotropic drugs to affect gene mRNA expression has the potential to modify the course of PD with either deleterious or therapeutic potential. Though it has been argued that genes correlate weakly with PD, the risk genes considered here are nonetheless significantly associated with PD, and have been demonstrated to affect PD risk at a statistical level, even if not well understood in terms of their biological significance. On the other hand, although some of the mutations and genes of interest have not yet demonstrated statistically significant relations to PD risk, they remain nonetheless of interest because of their putative pathobiological significance, and so they are also considered here. Thus, the genes considered in this report are either of statistical or biological significance in PD. Therefore, the effects of psychotropics, commonly used in treating patients with PD, on the transcription of these genes are of potential clinical interest and prompted this study.

2.0 Methods

2.1 Genes And Drugs Search Approach

The author comprehensively surveyed gene expression as a function of psychotropic treatment for genes associated with PD including classical mutation genes, risk-associated genes, and genes of interest by assessing literature in the PubMed database and data in the Gene Expression Omnibus Profiles database, last accessed on February 1, 2012. Search terms for drugs in these two databases were the drug categories and specific drugs detailed in Introduction Section 1.0
paragraph 3, drugs chosen because they represent common first-line treatments in the United States of America, and specific genes searched in these databases immediately follow.

*Classical mutation genes* included PARK1-16 mutations associated with PD (Gasser, 2009). Specifically, these are: Parkinson disease, familial 1 (PARK1), parkinson protein 2, E3 ubiquitin ligase (parkin) (PARK2), Parkinson disease 3 (autosomal dominant, Lewy body) (PARK3), Parkinson disease (autosomal dominant, Lewy body) 4 (PARK4), ubiquitin carboxyl-terminal esterase L1 (PARK5), Parkinson disease (autosomal recessive) 6 (PARK6), parkinson protein 7 (PARK7), Parkinson disease (autosomal dominant) 8 (PARK8), Parkinson disease (autosomal recessive) 9 (PARK9), Parkinson disease 10 (susceptibility) (PARK10), Parkinson disease (autosomal recessive, early onset) 11 (PARK11), Parkinson disease 12 (susceptibility) (PARK12), HtrA serine peptidase 2 (PARK13), phospholipase A2, group VI (cytosolic, calcium-independent) (PARK14), F-box protein 7 (PARK15), and Parkinson disease 16 (susceptibility (PARK16).

*Risk-associated genes* consisted of those most strongly associated with PD according to the PDGene database (Lill et al., 2012 <http://www.pdgene.org/>): microtubule-associated protein tau / saitohin (MAPT/STH), synuclein, alpha (SNCA), acid beta-glucosidase (GBA), leucine-rich repeat kinase 2 (LRRK2), peptidase M20 domain containing 1 (PM20D1), cyclin G associated kinase (GAK), methylcrotonoyl-coenzyme A carboxylase I (MCCC1), lysosomal-associated membrane protein 3 (LAMP3), serine threonine kinase 39 (STK39), bone marrow stromal cell antigen 1 (BST1), glycoprotein (transmembrane) nmb (GPNMB), SET domain containing 1A (SETD1A), genome-wide association at 8p22 (GWA_8p22), synaptotagmin XI / member RAS
oncogene family (SYT11/RAB25), family with sequence similarity 47, member E (FAM47E),
major histocompatibility complex, class II, DR beta 5 (HLA-DRB5), coiled-coil domain
containing 62 / huntingtin interacting protein 1 related (CCDC62/CHIP1R),
aminoacarboxymuconate semialdehyde decarboxylase / transmembrane protein 163
(ACMSD/TMEM163), and mediator complex subunit 13 (MED13). These risk – associated
genes generally exceed a level of $10^{-8}$ significance, range as high as $10^{-52}$, and their risk –
associated odds ratios are provided in Table 1. Descriptions of specific ethnic samples are
available on the PDGene website (Lill et al., 2012). Sample sizes used in the meta-analyses that
define the relationship of these genes to PD risk range from 677 to 53,380 subjects, with a mean
of 17,258.

*Genes of interest* were selected because they have at various points been associated with PD risk
in the PDGene database (Lill et al., 2012) or have emerged in recent meta-analyses of genome-
wide association studies (International Parkinson Disease Genomics Consortium et al., 2011) and
include nuclear casein kinase and cyclin-dependent kinase substrate 1 (NUCKS1), solute carrier
family 41, member 1 (SLC41A1), solute carrier family 45, member 3 (SLC45A3), pleckstrin
homology domain containing, family M (with RUN domain) member 1 (PLEKHM1),
diacylglycerol kinase, theta 110kDa (DGKQ), ubiquitin specific peptidase 24 (USP24),
GWA_12q23.3, superoxide dismutase 2, mitochondrial (SOD2), brain-derived neurotrophic
factor (BDNF), pyridoxal (pyridoxine, vitamin B6) kinase (PDXK), GWA 7p14.2,
apolipoprotein E (APOE), dopamine receptor D3 (DRD3), methylenetetrahydrofolate reductase
(NAD(P)H) (MTHFR), GWA 2q36.3, glutathione S-transferase mu 1 (GSTM1), major
histocompatibility complex, class II, DR alpha (HLA-DRA), PTEN induced putative kinase 1
(PINK1), fibroblast growth factor 20 (FGF20), solute carrier family 6 (neurotransmitter transporter, dopamine), member 3 (SLC6A3), cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6), GLIS family zinc finger 1 (GLIS1), monoamine oxidase B (MAOB), 28kDa calbindin 1 (CALB1), FERM, RhoGEF (ARHGEF) and pleckstrin domain protein 1 (chondrocyte-derived) (FARP1), low-density lipoprotein receptor-related protein 8 (LRP8), and dopamine receptor D2 (DRD2). Additionally, Liu et al. (2011) recently identified genes with genome wide significance in the range of $p<10^{-5}$ specifically within the Ashkenazi Jewish population: solute carrier family 25, member 48 (SLC25A48), unc-13 homolog B (UNC13B), solute carrier organic anion transporter family member 3A1 (SLCO3A1), wingless-type MMTV integration site family, member 3 (WNT3), and N-ethylmaleimide-sensitive factor (NSF). 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 psychopharmacological category and specific names in each database. Only reports of chronic administration (at least 3 weeks duration in animal studies) are considered here. (Studies of prenatal exposure, primarily involving anticonvulsants, are not considered.)

2.2 Analysis Of GEO Profiles Data
Gene expression data in GEO Profiles were considered if a given treatment was compared to untreated controls under the same experimental conditions and if the data involved at least 2 determinations at a single locus. Gene expression data was found for the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine (mouse hippocampus by Affymetrix GeneChip® Mouse Genome 430 2.0 Array after 21 day treatment (GEO Profiles accession number GDS2803) (Miller et al., 2008)), the neuroleptic antipsychotic haloperidol and atypical antipsychotic clozapine (mouse whole brain by Affymetrix GeneChip® Murine Genome U74 Version 2 Array [MG_U74Av2] after 4 week treatment (GDS2537) and by Affymetrix GeneChip® Mouse Expression 430A Array [MOE430A] after 12 week treatment (GDS2531)), and the atypical antipsychotic olanzapine (rat hippocampus by Affymetrix GeneChip® Rat Genome 230 2.0 Array after 21 day treatment (GDS2608) (Fatemi et al., 2006)). GEO Profiles data were analyzed by a one-way ANOVA with Bonferroni correction.

Probe sets in GEO Profiles allow quantification of upregulation or downregulation of a given gene. Reporting of findings is limited to genes where specific probe sets of these genes were upregulated or downregulated by at least 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 (i.e., greater than a 20% change from untreated control values), probe sets were assessed and compared with each other to determine their reliability in assaying gene expression. Results are provided for genes for which changes in expression were observed after determining that the probe set showing a change was in fact a reliable probe of the gene’s transcription.
Normalized expression data in GEO Profiles were derived from a gene chip and remain to be confirmed by quantitative real time polymerized chain reaction (RT-PCR) or other analyses.

3.0 Results

3.1 General Findings

Relevant results in PubMed were found for PARK2 (PRKN, parkin), PARK5 (UCHL1), BDNF, DRD3, MAOB, LRP8, and DRD2. PubMed revealed no relevant gene expression data for most of the classical mutation genes (PARK 1/PARK4 (SNCA), PARK3, or PARK6-16), a number of risk associated genes (MAPT/STH, GBA, LRRK2, PM20D1, GAK, MCCC1/LAMP3, BST1, GPNMB, SETD1A, GWA_8p22, SYT11/RAB25, FAM47E, HLA-DRB5, CCDC62/HIP1R, ACMSD/TMEM163, or MED13), or for many of the genes of interest including (NUCKS1, SLC41A1, SLC45A3, PLEKHM1, DGKQ USP24, GWA_12q23.3, SOD2, PDXK, GWA 7p14.2, APOE, MTHFR, GWA 2q36.3, GSTM1, HLA-DR2, PINK1, FGF20, SLC6A3, CYP2D6, GLIS1, CALB1, FARPI, SLC25A48, UNC13B, SLCO3A1, WNT3, or NSF).

Relevant results in GEO Profiles were found for PARK2 (PRKN, parkin), PARK5 (UCHL1), MAPT, GBA, MCCC1, SETD1A, CCDC62, HIP1R, TMEM163, BDNF, GSTM1, CALB1, SLCO3A1, and UNC13B. GEO Profiles revealed no gene expression data for PARK 3, PARK10-12, PARK 14-16, HLA-DRB5, GWA_12q23.3, MTHFR, GWA7p14.2, GWA2q36.3, HLA-DRA, or SLC25A48. Although expression data were available in GEO Profiles, data analysis demonstrated no appreciable effects by fluoxetine, haloperidol, olanzapine, or clozapine on the classical mutation genes PARK1/PARK4 (SNCA), PARK6-9, and PARK13, risk
associated genes SNCA, LRRK2, PM20D1, GAK, LAMP3, STK39, BST1, GPNMB, SYT11, RAB25, ACMSD, and MED13, or genes of interest NUCKS1, SLC41A1, SLC45A3, PLEKHM1, DGKQ, USP24, SOD2, PDXK, APOE, DRD3, FGF20, SLC6A3, CYP2D6, GLIS1, MAOB, FARP1, LRP8, DRD2, WNT3, or NSF, although there were no data for fluoxetine for ACMSD or TMEM163, 4-week haloperidol or clozapine for GAK, LAMP3, 4- and 12-week haloperidol or clozapine for CCDC62, ACMSD, MED13, MAOB or PLEKHM1, or for olanzapine or 4-week haloperidol and clozapine for FARP1, LRP8, GPNMB, or DGKQ, or for olanzapine alone for SETD1A or WNT3. Olanzapine data were compromised by lack of
detection call (a measure of reliability) for MCCC1, LAMP3, SYT11, RAB25, HIP1R, ACMSD, TMEM163, PDXK, DRD3, SLC6A3, GPNMB, and DRD2.

Positive findings (i.e., changes of at least 20% in mRNA expression) in GEO Profiles were thus restricted to TMEM163, GSTM1, and SLCO3A1 for olanzapine, and PARK5 (UCHL1), MAPT, GBA, MCCC1, SETD1A, CCDC62, HIP1R, BDNF, GSTM1, CALB1, UNC13B, and SLCO3A1 for fluoxetine. Only positive findings from the literature and GEO Profiles searches are summarized below.

3.2 Classical Mutations

PARK2 (PRKN, parkin, 6q25.2-q27). Mutations are associated with sporadic PD and with recessive early onset, slowly progressive, parkinsonism lacking Lewy bodies. Four weeks of haloperidol induced mRNA in rat striatum (Nakahara et al., 2001) in contrast to rat whole-brain negative findings (i.e., <20% change) in GEO Profiles, suggesting upregulation specific to the nigrostriatal system.
PARK5 (UCHL1, 4p14). Mutations are linked to autosomal dominant, levodopa - responsive PD with onset in the 6th decade. Chronic antipsychotic treatment in schizophrenia downregulated UCHL1 mRNA in the prefrontal cortex relative to matched healthy controls and drug-naïve patients (Vawter et al., 2001). In GEO Profiles, fluoxetine upregulated PARK5 expression by a factor of 1.33 (i.e., 33% upregulation) at probe set ID 1448260_at (NCBI reporter NM_011670), the only probe set used in the investigation.

3.3 Risk Associated Genes

MAPT (microtubule-associated protein tau, 17q21.1). Increased promoter region function, especially with the H1 haplotype, is associated with late-onset PD. In GEO Profiles, fluoxetine downregulated Mapt by a factor of 0.75 (i.e., 25% downregulation) at 1455028_at (BQ178510), the probe set with the greatest identity (97.54), although less so (0.81, 0.85, 0.88) at less specific probe sets.

GBA (acid beta-glucosidase, 1q21). GBA mutations are linked to PD. In GEO Profiles, fluoxetine upregulated Gba expression at both probe sets studied, by a factor of 1.30 at 1450099_a_at (NM_008094) and 1.36 at 1437044_a_at (BB241507).

MCCC1 (methylcrotonoyl-coenzyme A carboxylase I (alpha), 3q27). PD risk has been mapped to an intergenic single nucleotide polymorphism (SNP) in this area. In GEO Profiles, fluoxetine downregulated Mccc1 expression at both probe sets studied, by a factor of 0.79 at 1417227_at (NM_023644) and 0.78 at 1458208_s_at (BB770903).
SETD1A (SET domain – containing protein 1A, 16p11.2). SETD1A is a histone 3 lysine 4 methyltransferase that methylates H3 histones to activate transcription and is linked to PD. In GEO Profiles, although fluoxetine downregulated Setd1a expression at 1450336_at (NM_010940), this probe set was far less well annotated and had a poorer identity (36.98) than 1427116_at (C87155; identity 94.68), which showed only a 10% downregulation.

CCDC62/HIP1R (coiled-coil domain containing 62, 12q24.31; huntingtin interacting protein 1 related, 12q24). PD risk has been linked to an intronic SNP in CCDC62. In GEO Profiles, fluoxetine upregulated Ccdc62 at AI661708 by 1458644_at (1.23), the only probe set studied. Fluoxetine also upregulated Hip1r by a factor of 1.21 at AA590970 by 1425551_at, but not at two other probe sets of the same reporter (1458208_s_at (0.98) and 1425553_s_at (1.01)). All three Hip1r probe sets had identities of 98.64 and coverages of 98.6, and each lacked cross-hybridizing transcripts.

TMEM163 (transmembrane protein 163, 2q21.3). An intronic TMEM163 SNP is linked to PD risk. In GEO Profiles, olanzapine upregulated Tmem163 by a factor of 1.28 at BI293607 by 1382222_at. The only other probe set data (AW251322 by 1375398_at) was compromised by lack of detection call in all cells.

### 3.4 Genes Of Interest

**BDNF** (brain-derived neurotrophic factor, 11p13). A rare functional G196A (Val66Met) BDNF variant is associated with early onset PD. Among antipsychotic medications, the rat literature
reveals hippocampal and cortical Bdnf mRNA downregulation with haloperidol (Bai et al., 2003; Lipska et al., 2001; Park et al., 2009) (one study showed no change (Keilhoff et al., 2010)), both upregulation (Bai et al., 2003) and downregulation (Lipska et al., 2001) with clozapine (10mg/kg for 28 days (Bai et al., 2003; Lipska et al., 2001)), upregulation with olanzapine (Bai et al., 2003), quetiapine (Park et al., 2006), and lurasidone (Fumagalli et al., 2011), and no effect with risperidone (Keilhoff et al., 2010) or ziprasidone (Park et al., 2009). Chronic paliperidone upregulated Bdnf mRNA in rat hippocampal CA1/2, CA3, and dentate gyrus in rats (Hanson et al., 2011). In primate prefrontal cortex however, neither long-term treatment with haloperidol in monkeys (Hashimoto et al., 2005) nor chronic antipsychotic treatment in schizophrenia affected BDNF mRNA expression (Wong et al., 2010).

The mood stabilizer lithium downregulated hippocampal Bdnf mRNA expression in adult rats (Hanson et al., 2011; Jacobsen et al., 2004) and in ovariectomized mice (Valdes et al., 2010), but upregulated it in the cortex of these mice (Valdes et al., 2010). Chronic treatment with the mood stabilizing anticonvulsant carbamazepine upregulated BDNF mRNA expression in rat frontal cortex (Chang et al., 2009).

In rats treated for 21 days, the antidepressants imipramine (Larsen et al., 2008; Rogóz et al., 2007), sertraline (Nibuya et al., 1995), paroxetine (Martínez-Turrillas et al., 2005), venlafaxine (Larsen et al., 2008), and duloxetine (Calabrese et al., 2007; Molteni et al., 2009) each upregulated BDNF mRNA expression. Among tricyclic antidepressants (TCAs), chronic imipramine treatment upregulated hippocampal dentate gyrus Bdnf above the elevation in dentate and CA3 area associated with the chronic unpredictable stress rat model of depression.
(Larsen et al., 2010). Desipramine given for 21 days upregulated Bdnf in rat hippocampus
(Dwivedi et al., 2006; Jacobsen et al., 2004; Li et al., 2000; Nibuya et al., 1995) and frontal
cortex (Dwivedi et al., 2006) but, in two studies, downregulated hippocampal mRNA
(Torregrossa et al., 2005) and had no effect on cortex (Jacobsen et al., 2004; Torregrossa et al.,
2005). Neither chronic amitriptyline in mice undergoing spinal nerve transection (Hu et al.,
2010) nor chronic nortriptyline in Sprague Dawley rats (Hansson et al., 2011) increased
hippocampal Bdnf mRNA above control levels.

Among selective serotonin reuptake inhibitors (SSRIs), fluoxetine administered for 21 days
upregulated Bdnf mRNA in rat hippocampus (Dwivedi et al., 2006; Molteni et al., 2006;
Musazzi et al., 2009) (but without effect in two studies (Hanson et al., 2011; Torregrossa et al.,
2005)), visual cortex (Vetencourt et al., 2011), and in ventral tegmental area and nucleus
accumbens shell although this was not evident in substantia nigra or striatum (Molteni et al.,
2006). Chronic fluoxetine administration increased hippocampal BDNF mRNA expression in
C57BL/6 mice but not in BALB/c mice (Farley et al., 2012). Increased expression in visual
cortex was linked to reduced expression of the histone deacetylase Hdac5 and increased histone
acetylation of the promoter region of the Bdnf gene (Vetencourt et al., 2011). In adult male
Wistar rats, 8 weeks of fluoxetine treatment did not, however, alter brainstem BDNF gene
expression (Shishkina et al., 2012). In the glucocorticoid receptor impaired transgenic mouse
model of affective disorder, chronic treatment with fluoxetine reversed the model’s hippocampal
Bdnf mRNA downregulation (Pažanis et al., 2010). The SSRI fluvoxamine administered for 6
weeks to augment antipsychotic treatment in schizophrenic patients with prominent negative
symptoms upregulated peripheral mononuclear cell BDNF that increased over the treatment
course (Silver et al., 2011). Although chronic escitalopram did not affect hippocampal Bdnf expression in rats (Hansson et al., 2011; Jacobsen et al., 2004), 12 week treatment increased leukocyte BDNF mRNA expression, correlating with serum BDNF level and symptomatic improvement, in patients with depression (Cattaneo et al., 2010).

The norepinephrine-dopamine reuptake inhibiting antidepressant bupropion downregulated hippocampal Bdnf mRNA expression when chronically administered to Sprague Dawley rats (Torregrossa et al., 2005). The serotonin – norepinephrine reuptake inhibitor (SNRI) venlafaxine upregulated hippocampal dentate gyrus Bdnf mRNA above control levels in rats subjected to chronic unpredictable stress as a model of depression (Larsen et al., 2010), although venlafaxine was not found to change Bdnf mRNA expression in rats under more conventional conditions (Calabrese et al., 2011). The SNRI duloxetine upregulated reduced BDNF coding exon IX mRNA expression in the hippocampus and prefrontal cortex after chronic administration in a serotonin transporter knockout rat model of depression, although this did not correlate with BDNF protein levels in frontal cortex (Calabrese et al., 2010).

An antidepressant with melatonin MT1 and MT2 receptor agonist and 5HT2 receptor antagonist properties, agomelatine, has upregulated hippocampal in rats (Calabrese et al., 2011) and in the glucocorticoid receptor impaired mouse model of affective disorder (Païzanis et al., 2010), but not in prefrontal cortical Bdnf in rats (Calabrese et al., 2011). In patients with schizophrenia that had been treated with antidepressants, BDNF mRNA expression in dorsolateral prefrontal cortex, parietal cortex, and hippocampus was upregulated, in contrast to schizophrenic untreated controls (Wong et al., 2010).
In GEO Profiles, chronic fluoxetine upregulated Bdnf expression robustly at the only two probe sets studied, by a factor of 5.04 at 1422169_a_at (AY057913) and 4.45 at 1422168_a_at (AY057913).

**DRD3** (dopamine receptor D3, 3q13.3). It is not entirely clear how DRD3 affects PD risk although DRD3 mRNA is reduced in PD lymphocytes, unrelated to treatment. Although haloperidol for 21 days did not affect rat lymphocyte Drd3 mRNA expression (Caronti et al., 1999), rat brain studies demonstrate that chronic haloperidol (Buckland et al., 1992; D'Souza et al., 1997), loxapine (Buckland et al., 1992; D'Souza et al., 1997), clozapine (D'Souza et al., 1997), and pimozide (D'Souza et al., 1997), each upregulated whole brain D3 mRNA after 32 days. In human lymphocytes as in rat lymphocytes, antipsychotic treatment did not affect DRD3 expression in patients with schizophrenia or bipolar disorder (Ilani et al., 2001; Vogel et al., 2004). After chronic administration of at least 21 days, amitriptyline, desipramine, imipramine, fluoxetine, tranylcypromine, and electroconvulsive therapy each upregulated D3 mRNA expression in the nucleus accumbens shell (Lammers et al., 2000).

**GSTM1** (glutathione S-transferase mu 1, 1p13.3). The GSTM1 null genotype is linked to PD in the contexts of CYP2D6 poor metabolizer status and solvent exposure. In GEO Profiles, fluoxetine downregulated Gstm1 expression by a factor of 0.77 at 1448330_at (NM_010358) and 0.82 at 1416416_x_at (NM_010358), but not at probe sets with significantly lesser identities (0.99 at 1425626_at and 0.92 at 1425627_x_at). Olanzapine upregulated Gstm1 expression by a factor of 1.20 at 1386985_at (M28241), the only probe set studied.
**MAOB** (monoamine oxidase B, Xp11.23). The MAOB G genotype is variably associated with PD risk, especially in men. Risperidone (Chen et al., 2005, 2007) and olanzapine (Chen et al., 2007) (but not haloperidol or clozapine (Chen et al., 2007)) treatment for 4 weeks in rats upregulated frontal cortical Maob expression.

**CALB1** (28kDa calbindin 1, 8q21.3-q22.1). The CALB1 SNP rs1805874 is linked to PD risk. In GEO Profiles, chronic fluoxetine downregulated Calb1 expression at all probe sets studied, by a factor of 0.73 at 1417504_at (BB246032), 0.45 at 1448738_at (BB246032), 0.50 at 1456934_at (BB177770), and 0.66 at 1458836_at (AW557885), with 1417504_at being the best supported with an identity of 95.56.

**LRP8** (low-density lipoprotein receptor-related protein 8, 1p34). LRP8 knockout increases tau phosphorylation in mice, suggesting a relation to MAPT. Antipsychotic administration downregulated ApoER2 (LRP8) mRNA in peripheral lymphocytes after 6 months of treatment compared to pre-treatment baseline in drug-naive patients with schizophrenia (Suzuki et al., 2008).

**DRD2** (dopamine receptor D2, 11q23). Knockout in mice produces parkinsonism, and the TaqIa polymorphism, especially the A1A1 genotype, and 15-allele polymorphism are linked to PD motor fluctuation risk. DRD2 deficient mice manifest akinesia and bradykinesia resembling PD. In post-mortem brains of patients with schizophrenia treated with antipsychotics, some dying of suicide, frontal cortical DRD2 mRNA was similar to normal controls (Urígüen et al., 2009) and
untreated schizophrenia (Tallerico et al., 2001). Although several early studies did not find murine striatal D2 mRNA expression changes after chronic haloperidol treatment (Matsunaga et al. 1991; Srivastava et al., 1990; van Tol et al., 1990), subsequent studies found upregulation (Bernard et al., 1991; Buckland et al., 1992, 1993; Fishburn et al., 1994; Jaber et al., 1994; Rogue et al., 1991). In rats, 32-day treatment with antipsychotics dose-dependently upregulated D2 mRNA expression in the striatum (haloperidol), prefrontal cortex (haloperidol), and whole brain (loxapine) (Buckland et al., 1993; D'Souza et al., 1997). In rat pituitary, 21 days of haloperidol upregulated, aripiprazole downregulated, and clozapine did not affect D2 mRNA expression (Inoue et al., 1998). In the ventral tegmental area, both aripiprazole and olanzapine increased D2 mRNA expression after 12 weeks of treatment (Han et al., 2009). Six-months treatment with chlorpromazine, haloperidol, molindone, pimozide, risperidone, olanzapine, and clozapine upregulated prefrontal and temporal cortical D2 mRNA expression in primates, but in contrast to the other drugs, clozapine and olanzapine did not affect striatal DRD2 expression (Lidow et al., 1997). Chronic lithium treatment and lithium withdrawal did not affect D2 mRNA expression in the ventral tegmental area (Ferrie et al., 2008). Chronic treatment with amitriptyline or imipramine, but not desipramine, fluoxetine, tranylcypromine, or electroconvulsive treatment, increased D2 mRNA expression in rat striatum (Lammers et al., 2000). Thus, antipsychotics and tertiary amine tricyclic antidepressants upregulate Drd2 mRNA in at least one brain site, with haloperidol, other neuroleptics, and certain tricyclics upregulating striatal Drd2 mRNA.

**UNC13B** (unc-13 homolog B (C. elegans), 9p13.3). The protein product is involved in priming synaptic vesicular exocytosis via syntaxin, and in regulating neurotransmission
(Liu et al. 2011). Renal cells transfected with this gene and exposed to hyperglycemic –
induced increases in diacylglycerol undergo apoptosis. In GEO Profiles, fluoxetine
upregulated Unc138 by a factor of 1.39 at NM_021468 by 1417757_at (identity 97.57)
but only 1.03 at AV231882 by 1443308_at (identity 81.58).

SLCO3A1 (solute carrier organic anion transporter family, member 3A1, 15q26). The
protein product of this gene is enriched in brain glia and neurons, especially in frontal
cortical neuronal gray and white matter axons and soma, and has mediated the transport
of estrone-3-sulfate, prostaglandins E1 and E2, thyroxine, and vasopressin. It is likely
associated with neuronal signaling associated with reuptake mechanisms. In GEO
Profiles, olanzapine upregulated Slco3a1 by a factor of 1.47 at AI101171 by 1373734_at,
the only of 2 reporter data sets that had data cells not compromised by absent detection
calls. Nonetheless, even for this probeset, 2 of 4 data cells had absent detection calls,
indicating a need for confirmation.

4.0 Discussion
These findings indicate that psychotropic drugs commonly prescribed in PD can affect the
transcription of genes associated with the risk of developing PD when administered chronically
in animals and humans for at least 21 days, summarized by gene in Table 1 and by drug in the
abstract. Fluoxetine effects on BDNF and UCHL1 in GEO Profiles remained significant after
Bonferroni correction (Table 2), 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 PD management upon more specific analyses of the nigrostriatal system with more sensitive and reliable real time polymerized chain reaction (RT-PCR) using reverse transcription.

It must be emphasized that these data are reflective of an early and nascent heterogeneous literature involving uneven and unsystematic study of both genes and drugs. It is therefore premature to rely upon statistical analyses of these findings. Nevertheless, the statistical results are provided at this point only as an initial consideration for those who may be interested. It is important to recognize that this is an evolving dynamic literature, with the strength of gene associations fluctuating depending on the influence of forthcoming data.

Many of the genes mentioned here have not been well – studied, especially some of the newer more highly associated risk genes, and their relation to PD pathobiology is even still more cryptic at this point. Though it has been argued that genes correlate weakly with PD, the risk genes considered here are nonetheless significantly associated with PD, and have been demonstrated to affect PD risk at a statistical level, even if not well understood in terms of their biological significance. Thus, although the pathobiological relationship to PD of many of the risk genes is yet emerging, they are considered here because of their statistical relationship. In contrast, mutations and genes of interest are considered because of their putative biological relationship to PD and not because of their statistical properties.

Clearly, PD – associated genes are not the only genes affected by psychotropics, and transcriptional explorations in GEO Profiles of leading genes associated with type II
diabetes mellitus and antipsychotic – induced diabetes and weight gain (TCF7L2, PPARG, KCNJ11, IGF2BP2, HHEX, CDKAL1, SLC30A8, FTO, CNR1) revealed that IGF2BP2 exceeded the 20% threshold and was upregulated by a factor of 1.31 (Lim et al. 2010 http://t2db.khu.ac.kr:8080/; Irvin et al. 2009; Tiwari et al. 2010; Tiwari et al. 2011; Vehof et al. 2011). This is comparable to the transcriptional changes observed in the present study, instilling confidence that PD gene expression induced by psychotropics can potentially affect PD onset and progression in a clinically meaningful manner.

Functional analyses (haplotype, mutation severity, null alleles, and knock-out models) of MAPT, GBA, BDNF, and DRD2 indicate that fluoxetine, imipramine, certain other serotonergic antidepressants, atypical antipsychotics, and neuroleptics may attenuate PD risk whereas lithium and bupropion may augment PD risk (although these effects may differ in patients with specific mutations or variants such as the GBA mutation and G196A BDNF variant). The biological role of these genes (Figures 1 and 2) is currently incompletely understood and BDNF may relate more to neuroregeneration than to PD risk.

Most research to date has focused on cortical and hippocampal regions in this early literature, and the striatum and substantia nigra remain to be investigated. It should be kept in mind, however, that PD-associated genes themselves need not necessarily be affected within nigrostriatal tracts in order to exert their influence on PD risk because their risk may be mediated through interactions with other factors or genes yet to be discovered. There remains, however, a need to confirm these drug effects in research paradigms that are more clinically relevant to PD, described below.
It can nevertheless be said at this point that specific psychotropics may meaningfully alter the transcription of genes that are important to developing PD (inferred from the association of gene mutations and variants with PD risk). It is possible that transcriptional effects on these genes may affect PD risk and clinical progression, although this remains to be demonstrated since transcription may not correlate with protein concentration (e.g., lithium downregulates BDNF gene expression but increases BDNF (Jacobsen et al., 2004)).

Limitations of this investigation include problems inherent to an uneven, unsystematic, and emerging literature, and the limitations inherent to literature searches. Additionally, gene definitions, risk rankings, probe sets, gene functions, gene roles in PD, and expression data are evolving, meaning that the relevance of some of the current findings may become obsolete over time. The study of heterogeneous species, cross-species translational validity between rodents and humans, varying degrees of gene association in different PD populations and with Lewy body histopathology, and potentially differential gene or drug effects in different populations or at different PD stages provide the possibility that some of the findings summarized here may not apply in human PD or may be relevant only in certain PD subpopulations. Furthermore, reliance on a single technology in the GEO Profiles data (i.e., Affymetrix gene chips), multiple gene effects of a single drug that may vary in potency and by drug dose, gene – gene interactions, epigenetic interactions, and sometimes – conflicting findings in the literature may also impede the translation of these findings into clinically important effects. For example, although PRKN (PARK2) mutations are classically associated with parkinsonism lacking Lewy bodies, they can also be associated with Lewy body – positive parkinsonism (Farrer et al., 2001).
Also, PARK5 UCHL1 S18Y mutations have been pathogenic, protective, or without effect, depending upon the specific study (Maraganore et al., 2004). Although the classical mutations and genes of interest generally have low attributable risk for PD in contrast to the risk associated genes, and may or may not be causally linked to PD pathobiology, they are nevertheless empirically associated with PD risk and represent the best genetic correlates available to date. Furthermore, each risk gene variant has been replicated (except for PRKN) in a large number of subjects (except for GBA), with odds ratios ranging between 0.75 – 0.93 and 1.08 - 3.27. It additionally remains possible that medicines or other simultaneously expressed genes mask their apparent attributable risk for PD through epigenetic or gene – gene interactions, and that causal relevance will be forthcoming as PD pathobiology is further elucidated, increasing their relevance to PD risk and progression.

The current absence of established risk-modifying treatments, the frequency with which psychotropic drugs are used, and these initial promising findings prompt the need for further study of psychotropics on these genes that have already been established to confer risk in PD. Ideally, future study will include determinations of: (1) nigrostriatal gene expression in animals undergoing treatment with these drugs for at least 3 months; (2) the relative risk for PD in patients chronically treated with these drugs; (3) relative correlations of nigrostriatal transcription of target genes with transcription in other more readily – accessible proxy sites, such as peripheral monocytes, cerebrospinal fluid, etc.; (4) gene transcription at well – correlated proxy sites by RT-PCR in PD patients chronically treated with these agents at a stable dose for at least 3 months; and (5) study of other PD risk genes using these approaches, since extant data have not involved these methods and have, therefore, not excluded potential drug effects on these
genes. These approaches may help reduce confounds including cross-species translation, gene chip technology, and site-specific, time-dependent, and dose-related transcription effects. Effects of these drugs on the specific mutations and polymorphisms associated with PD risk are less clear and are likely to remain so until data sets of sufficient size can be analyzed.

There are of course many other effects of psychotropics that can impact multiple processes at the neuronal level (Lauterbach et al., 2010a,b; Lauterbach and Mendez, 2011), and gene expression is only one of many of these processes that can influence neurodegenerative outcome. Whether transcriptional effects will play an important role in neuroprotection remains to be determined. In any event, this report provides an initial framework to consider the potential impact of commonly prescribed drugs on genes that are relevant to PD. The effects of psychotropics on the expression of these genes should now be studied further as outlined above.

**Conclusion**

Psychotropics are widely prescribed for neuropsychiatric disorders in PD and affect a diverse array of genes, some of which are implicated PD pathobiology. The results of the present study indicate that first-line psychotropics used in managing patients with PD affect the transcription of genes that have been statistically and biologically linked to PD pathogenesis. Several antipsychotics and serotonergic drugs show potential to serve as neuroprotectants, while lithium and bupropion may foster progression, based on preliminary transcriptional effects of MAPT, GBA, CCDC62, HIP1R, BDNF, and DRD2, although multiple limitations apply to these findings. Clinical studies of these
drugs on these genes and on PD progression are now needed.

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Captions For Figures

Figure 1. **Intraneuronal Neurodegenerative Pathways.** Interactions of genes with Parkinson’s disease neuroprotective and neurodegenerative pathways. Relations terminating in an arrowhead indicate facilitation, those with double arrowheads indicate mutual facilitation, whereas dashed lines with bulbous terminations indicate inhibition. αSyn refers to alpha synuclein, tau to tau protein, and ROS to reactive oxygen species. Other terms refer to gene designations.

Figure 2. **Neuronal Viability Mechanisms.** Factors affecting the viability of nigrostriatal dopamine neurons and striatopallidal GABAergic neurons, leading to normal motor function and the absence of Parkinson’s disease manifestations. Relations terminating in an arrowhead indicate facilitation, and dashed lines terminating in a bulb indicate inhibition. αSyn refers to alpha synuclein, Aβ to beta-amyloid protein, tau to tau protein, and ROS to reactive oxygen species. Other terms refer to gene designations.
Supplementary Information For Figure 1

MAPT transcription produces tau protein, and LRP8 can negatively modulate MAPT activity. PARK1/4 (SNCA) transcription produces alpha-synuclein (αSyn), which can facilitate tau formation. αSyn and tau mutually facilitate their aggregation. αSyn inhibits apoptosis whereas mono-ubiquitylated αSyn translocates to the neuronal nucleus and is associated with apoptosis. Aggregated proteins including αSyn and tau can ultimately produce mitochondrial dysfunction, reactive oxygen species (ROS), and apoptosis, and can inhibit the proteasome. These and other aggregated or obsolete proteins are ubiquitylated and degraded in the proteasome. PARK5 (UCHL1) transcription regulates the availability of ubiquitin monomers while PARK2 (parkin) ligates ubiquitin tags to these proteins to signal proteasomal processing. PARK2 also attenuates ROS - induced inflammation. GSTM1 and CYP2D6 gene products promote solvent detoxification, and deficiencies in these proteins permit toxicity. GSTM1 becomes particularly important in the context of CYP2D6 dysfunction. Toxins and mitochondrial dysfunction can predispose to or cause apoptosis. The MAOB gene encodes monoamine oxidase B (MAOB), which can generate ROS when oxidizing dopamine and other molecules. ROS can produce mitochondrial dysfunction and inflammation, and vice versa. Ubiquitylated αSyn, damaged and aggregated proteins, toxins, proteasomal dysfunction, mitochondrial dysfunction, and ROS can each induce apoptosis, thereby killing the cell, while αSyn itself can deter apoptosis.

Supplementary Information For Figure 2

Toxins, inflammation, aggregated proteins (including αSyn, Aβ, and tau), apoptosis, reactive oxygen species (ROS), and mitochondrial dysfunction all lead to reduced cellular viability or death, including dopamine neurons. BDNF transcription produces the neurotrophin BDNF.
DRD3 transcription leads to dopamine D3 receptors, which have a role in regulating trophic support of substantia nigra neurons and their neurogenesis. The product of the HIP1R gene assists in maintaining neuronal presynaptic function while the effects of UNC13B and SLC03A1 are not yet clear. Although their mechanisms are currently cryptic, a variety of other genes (GBA, MCCC1, CCDC62, CALB1, ACMSD) also appear to support and protect nigrostriatal presynaptic neurons. DRD2 encodes the dopamine D2 receptor, borne on striatopallidal GABAergic neurons. The proper functioning of these striatal neurons is critical to normal motor function, and they are regulated by nigrostriatal dopamine acting on striatal D2 receptors.

Striatal neurons are supported and maintained by BDNF, other trophic and neurogenic factors, and by the product of the TMEM163 gene, the mechanism for which awaits discovery. Loss of presynaptic nigrostriatal neuron dopamine release on striatal D2 receptors leads to the manifestations of Parkinson’s disease.
Figure 1

MAPT → Tau → Tau Aggregation → Toxicity

LRP8

PARK1/4 → αSyn → αSyn Aggregation → Mitochondrial Dysfunction

Obsolete Proteins

Ubiquitin

PARK5

PARK2

Ubiquitylated αSyn → Apoptosis

Ubiquitylation

Proteasome Dysfunction

Proteasome

ROS → MAOB

Inflammation
Table 1. Putative Effects Of Psychotropics On PD Risk By Gene

<table>
<thead>
<tr>
<th>Gene</th>
<th>OR (95% CI)</th>
<th>Chronic Drug Effects On Gene mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPT</td>
<td>0.78 (0.75 – 0.80)</td>
<td>Fluoxetine downregulates MAPT expression</td>
</tr>
<tr>
<td>GBA</td>
<td>3.27 (2.45 – 4.37)</td>
<td>Fluoxetine upregulates GBA expression</td>
</tr>
<tr>
<td>MCCC1</td>
<td>0.84 (0.80 – 0.89)</td>
<td>Fluoxetine downregulated MCCC1 expression</td>
</tr>
<tr>
<td>CCDC62 / HIP1R</td>
<td>1.17 (1.09 – 1.25)</td>
<td>Fluoxetine upregulated CCDC62 as well as HIP1R expression</td>
</tr>
<tr>
<td>ACMSD / TMEM163</td>
<td>1.40 (1.2 – 1.63)</td>
<td>Olanzapine upregulated TMEM163 expression</td>
</tr>
<tr>
<td>BDNF</td>
<td>1.12 (1.04 – 1.22)</td>
<td>Haloperidol, lithium, and bupropion, downregulate while olanzapine, quetiapine, lurasidone, paliperidone, carbamazepine, desipramine, fluoxetine, sertraline, paroxetine, fluvoxamine, s-citalopram, venlafaxine, duloxetine, and agomelatine upregulate BDNF expression</td>
</tr>
<tr>
<td>DRD3</td>
<td>1.08 (1.02 – 1.15)</td>
<td>Haloperidol, loxapine, pimozide, clozapine, amitriptyline, imipramine, desipramine, fluoxetine, tranylcypromine, and electroconvulsive therapy upregulate D3 expression</td>
</tr>
<tr>
<td>GSTM1</td>
<td>0.90 (0.83 – 0.98)</td>
<td>Fluoxetine downregulates whereas olanzapine upregulates GSTM1 expression</td>
</tr>
<tr>
<td>UCHL1 (PARK5)</td>
<td>0.93 (0.87 – 0.99)</td>
<td>Antipsychotics downregulate whereas fluoxetine upregulates UCHL1 mRNA</td>
</tr>
<tr>
<td>PRKN (PARK2)</td>
<td>0.79 (0.64 – 0.97)</td>
<td>Haloperidol upregulates parkin expression</td>
</tr>
<tr>
<td>MAOB</td>
<td>1.10 (1.01 – 1.2)</td>
<td>Risperidone and olanzapine upregulate MAOB expression</td>
</tr>
<tr>
<td>CALB1</td>
<td>0.89 (0.8 – 0.99)</td>
<td>Fluoxetine downregulates Calb1 expression</td>
</tr>
<tr>
<td>LRP8</td>
<td>0.93 (0.87 – 0.99)</td>
<td>Antipsychotics downregulate expression</td>
</tr>
<tr>
<td>DRD2</td>
<td>1.17 (1.01 – 1.36)</td>
<td>Chlorpromazine, haloperidol, loxapine, molindone, pimozide, risperidone, olanzapine, clozapine, aripiprazole, amitriptyline, and imipramine upregulate expression</td>
</tr>
<tr>
<td>UNC13B</td>
<td>0.49 (0.34 – 0.69)</td>
<td>Fluoxetine upregulates Unc13b</td>
</tr>
<tr>
<td>SLCO3A1</td>
<td>1.84 (1.38 – 2.47)</td>
<td>Olanzapine upregulates Slco3a1 expression</td>
</tr>
</tbody>
</table>

Legend for Table 1. Risk ranking (low number signifies a relatively strong association with PD), cumulative odds ratio of association (and 95% confidence interval) with PD for the relevant

Table 1 & 2
mutation, allele, or polymorphism, and effects of specific drugs on gene mRNA expression are displayed.

Table 2. Statistical Analysis Of Gene Data In GEO Profiles

<table>
<thead>
<tr>
<th>Gene</th>
<th>Probe Set</th>
<th>Mean (Controls)</th>
<th>Mean (Treated)</th>
<th>F Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARK5</td>
<td>1448260_at</td>
<td>7184.45 ± 28.50</td>
<td>9569.03 ± 109.30</td>
<td>891.266</td>
<td>0.0011 *</td>
</tr>
<tr>
<td>MAPT</td>
<td>1455028_at</td>
<td>1296.61 ± 122.60</td>
<td>974.60 ± 31.15</td>
<td>12.961</td>
<td>0.069</td>
</tr>
<tr>
<td>GBA</td>
<td>1450999_a_at</td>
<td>358.29 ± 13.19</td>
<td>467.74 ± 3.72</td>
<td>127.485</td>
<td>0.0077</td>
</tr>
<tr>
<td></td>
<td>1437044_a_at</td>
<td>278.90 ± 2.18</td>
<td>380.08 ± 38.04</td>
<td>13.829</td>
<td>0.065</td>
</tr>
<tr>
<td>MCCC1</td>
<td>1417227_at</td>
<td>277.25 ± 14.89</td>
<td>219.01 ± 22.84</td>
<td>9.126</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>1458208_s_at</td>
<td>210.46 ± 16.15</td>
<td>164.90 ± 16.13</td>
<td>7.969</td>
<td>0.106</td>
</tr>
<tr>
<td>CCDC62</td>
<td>1458644_at</td>
<td>9.05 ± 0.58</td>
<td>11.11 ± 2.25</td>
<td>1.579</td>
<td>0.33</td>
</tr>
<tr>
<td>HIP1R</td>
<td>1425551_at</td>
<td>74.68 ± 6.72</td>
<td>90.35 ± 8.18</td>
<td>4.38</td>
<td>0.17</td>
</tr>
<tr>
<td>BDNF</td>
<td>1422169_a_at</td>
<td>62.69 ± 20.02</td>
<td>316.28 ± 18.05</td>
<td>176.976</td>
<td>0.0056†</td>
</tr>
<tr>
<td></td>
<td>1422168_a_at</td>
<td>610.92 ± 24.71</td>
<td>2720.59 ± 29.32</td>
<td>6053.45</td>
<td>0.00017 *</td>
</tr>
<tr>
<td>GSTM1</td>
<td>1448330_at</td>
<td>2387.97 ± 110.71</td>
<td>1829.22 ± 138.64</td>
<td>19.836</td>
<td>0.046</td>
</tr>
<tr>
<td></td>
<td>1416416_x_at</td>
<td>2417.96 ± 106.94</td>
<td>1995.63 ± 33.71</td>
<td>28.376</td>
<td>0.047</td>
</tr>
<tr>
<td>CALB1</td>
<td>1417504_at</td>
<td>5016.29 ± 198.91</td>
<td>3665.31 ± 250.87</td>
<td>35.613</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td>1448738_at</td>
<td>364.01 ± 27.83</td>
<td>164.09 ± 27.40</td>
<td>52.4</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>1456934_at</td>
<td>264.96 ± 26.13</td>
<td>132.68 ± 26.51</td>
<td>25.257</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>1458836_at</td>
<td>9.73 ± 3.64</td>
<td>6.44 ± 0.95</td>
<td>1.524</td>
<td>0.34</td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMEM163</td>
<td>1382222_at</td>
<td>325.73 ± 71.46</td>
<td>415.60 ± 121.73</td>
<td>1.621</td>
<td>0.24</td>
</tr>
<tr>
<td>GSTM1</td>
<td>1386985_at</td>
<td>656.129 ± 52.43</td>
<td>786.72 ± 144.82</td>
<td>2.875</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Legend for Table 2. Statistical analysis by ANOVA of gene expression in GEO Profiles.

Asterisks indicate results significant after Bonferroni correction (alpha = 0.0031 for fluoxetine, 0.025 for olanzapine); the dagger indicates non-significant trend after Bonferroni correction.

UNC13B and SLC03A1, identified in Ashkenazi populations, were not included in these analyses.