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Psychotropic Idiosyncratic Drug Reactions: A Brief Review of Proposed Mechanisms

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ABSTRACT

Background: *Idiosyncratic drug reactions are unpredictable events known to produce serious morbidity and mortality. There is little understanding of the pathophysiology underlying these adverse effects, specifically with psychotropic medications.*

Material and Methods: *A literature search were conducted in Pubmed and Cochrane by using the following terms in varying combinations: idiosyncratic reactions, fluphenazine, chlorpromazine, escitalopram, clozapine, risperidone, quetiapine, olanzapine, sertraline, duloxetine, amitriptyline, nortriptyline, valproic acid, carbamazepine, drug induced liver injury, agranulocytosis, genome site, and polymorphism. Case reports were excluded in order to have a review with articles reflective of a strong sample size. The Food and Drug Administration was contacted for updates on pre-existing knowledge on idiosyncratic reactions. Our intention was to analyze and to integrate the proposed mechanisms from the existing scientific literature.*

Results: *Reported frequencies of idiosyncratic drug reactions range from an upper limit of 5% to as low as 1 in 10,000 to 100,000 individuals. However, these data are mostly based upon reports describing non-psychotropic medications. Postulated mechanisms of idiosyncratic drug reactions include immune mediated and non-immune mediated types. Suggested mechanisms are explored with emphasis on drug induced liver injury and agranulocytosis reactions with chlorpromazine and clozapine, respectively.*

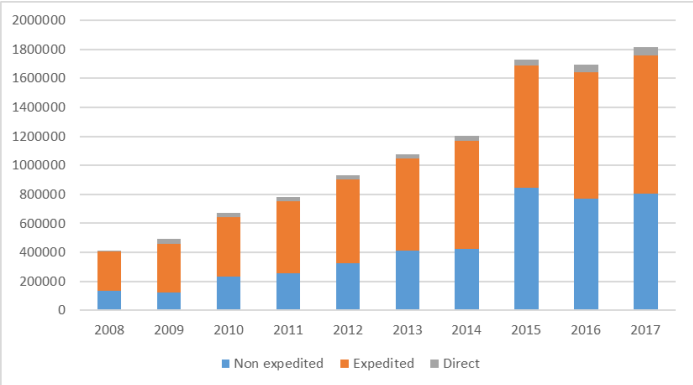
Conclusion: *Idiosyncratic drug reactions are rarely, if ever, detected during randomized controlled trials, usually emerging during post marketing surveillance. More mechanistic studies are needed so that a better understanding of the underlying pathophysiologic processes can be obtained, and improved surveillance can be implemented. Recently developed techniques (including homology modeling, docking simulations, and quantitative systems pharmacology) will be instrumental in the aforementioned process.*

Keywords

Agranulocytosis, Drug induced liver injury, Genome site, Idiosyncratic reactions, Psychotropics.

Adverse events are undesirable experiences associated with the use of any medical product, broadly categorized into type A and type B reactions. Type A reactions are common dose-related events usually identified in pre-clinical and clinical trials, that have been extensively studied. On the other hand, type B reactions, commonly known as idiosyncratic drug reactions (IDR), occur in a considerably smaller population independent of dose and time [1]. warranting greater concerns. Predominantly unpredictable and rare, IDRs account for about 6 to 10% of adverse drug events [2], with most IDR's going unreported, with no recognition. Furthermore, from 1975 to 2000, just over 10% of approved drugs in the United States had to be withdrawn or given a black box

warning due to unpredicted adverse events [3]. The total adverse events reported in 2017 in the United States were 1,796,239 and, except for 2016, have been increasing every year. (Table1).



	Non expedited	Expedited	Direct
2008	132687	273586	32896
2009	126172	329707	34166
2010	234672	408881	28944
2011	255232	498832	28043
2012	326586	577515	29021
2013	411411	634816	28390
2014	423744	746074	34232
2015	846702	839197	41659
2016	771026	869959	50993
2017	803516	951656	60566

Table 1: FDA adverse events reporting system (FAERS) Public Dashboard.

Non expedited reports do not meet the criteria for expedited reports and include cases that are reported as serious and expected, non-serious and unexpected, and non-serious and expected. Expedited reports contain at least one adverse event that is not currently described in the product labelling and for which the patient outcome is serious. Direct reports are voluntarily submitted directly to FDA through the MedWatch program by consumers and healthcare professionals.

Among the psychotropic agents, the ones noted to have the most prominent adverse effects are antipsychotics and mood stabilizers [4]. The well-known IDRs known to occur with psychotropic medications (PMs) are hepatotoxicity, neuroleptic malignant syndrome, major cardiovascular events, agranulocytosis, Steven-Johnson syndrome and genitourinary conditions like priapism [5].

IDR's, particularly those associated with PMs, investigated in prior studies have been proposed to have various mechanisms, with the majority of studies exploring clozapine-induced agranulocytosis and drug-induced liver injuries:

- Receptor blockade has been implicated as a causative factor for IDRs given that all antipsychotics block dopamine receptors.
- Chemical reactions at the molecular level are thought to contribute to IDRs, mediated through redox/oxidative stress reactions.
- Inflammatory and immune mediated mechanisms are suggested with evidence collected from animal studies, but few, if any, in human subjects.
- Specific polymorphisms in cytochromes and human leukocyte antigens (HLAs) have been observed and analyzed to be associated with IDRs.
- Ethnic differences have been noted based in the aforementioned polymorphisms.
- Lastly, an important discussion on studies done with methods of whole exome sequencing and utilizing other methods to identify variants linked to IDRs are discussed.

For some time, the famously explored reasons for IDRs included the hapten and the danger hypotheses. These hypotheses could only explain some adverse events. Newer biotechnological principles are being explored that focus on modeling 3D (dimensional) molecular structures that can provide more mechanistic clarity.

Given the aforementioned, it is essential to be aware of the mechanisms underlying IDRs. In this paper we discuss the hypotheses and data supported mechanisms that are published and the future possible methods for improved IDR recognition.

Method

A literature search was conducted on PubMed and Cochrane databases. Search terms included idiosyncratic drug reactions, fluphenazine, chlorpromazine, escitalopram, clozapine, risperidone, quetiapine, olanzapine, sertraline, duloxetine, amitriptyline, nortriptyline, valproic acid, carbamazepine, drug induced liver injury, agranulocytosis, genome site, and polymorphism. 282 articles were collected out of which 86 were deemed useful for this study. The food and drug administration (FDA) was contacted to receive further information on current updates of IDRs. One reference was based on personal communication.

Results

A general explanation proposed for IDRs is that they are immune mediated [6]. The following hypotheses have been broadly used to explain this categorization.

Hapten Hypothesis. According to the hapten hypothesis, a reactive drug metabolite binds covalently to a protein forming an irreversibly bound metabolite-protein complex. This is recognized as foreign by the antigen presenting cells (APCs), processed into peptide fragments and presented in the major histocompatibility complex (MHC) groove to T cells [6]. However, it is known that not all drugs known to have reactive metabolites generate IDRs.

Danger Hypothesis. Per the danger hypothesis, two signals are necessary to generate an IDR. The hypothesis postulates [6] that a foreign protein cannot generate a significant immune response unless there is an adjuvant present responsible for stimulating antigen presenting cells. In addition, a signal 2 is required to cause an immune response that is costimulation [6] of T cells by APCs, mediated by B7 on APCs and CD28 on T cells. The danger signal is believed to be an endogenous molecule [6] from stressed cells responsible for the stimulation of APCs. Therefore these danger

signals will be specific to the cell types and stressors. However, the signal 1 has not been clearly identified to be the drug, a drug modified peptide or an autoantigen [6].

The following discussion will draw upon and apply the hapten and danger hypotheses principles while adding data from subsequent studies to explain more clearly IDR mechanisms.

MEDICATION	GENOME SITE	PROPOSED MECHANISM	CLINICAL EFFECT
FPZ/CPZ/TRZ (Phenothiazines)	 Retinal P450 myeloperoxidase gene polymorphisms.	Metabolic activation to electrophiles→ocular adduct formation → inhibition of retinal redox homeostasis→cell death D2,D4 receptor blockade → retinal melatonin accumulation. Oxidation of heteroatoms of phenothiazines. Hydroxylation at position 7 of phenothiazine ring.	Retinopathy Hepatotoxicity
Clozapine	AHR agonists increase mRNA expression for FM-O3 synthesis MDR1 gene polymophisms of C3435T and G2677T polymorphisms Myeloperoxidase polymorphisms CYP2D6 polymorphisms	Increased FM-O3 synthesis that activates nitrenium ion Altering P-glycoprotein Single base substitution (G-463A) in myeloperoxidase promoter region → decreased transcription rate→ decreased myeloperoxidase activity Poor metabolizers	Agranulocytosis
CPZ	Sustained activation of JNK (TIRAP)	Inflammation increases the toxic response to CPZ	Hepatic cholestasis

Table 2: Idiosyncratic Drug Reactions to antipsychotic medications. FPZ= Fluphenazine; CPZ= Chlorpromazine; TRZ= Thioridazine; AHR= Arylhydrocarbon receptor; FM= Flavin monooxygenase.

Antipsychotics

Phenothiazines

It has been suggested [7] that aminopropyl or piperadine phenothiazines, that is chlorpromazine (CPZ) and thioridazine (TRZ), produce retinopathy through metabolic activation to electrophiles, directly forming ocular adducts, inhibiting retinal redox homeostasis and causing cell death. Having a similar structure, fluphenazine (FPZ) is postulated to have a similar mechanism. The retinal pigment epithelium expresses high levels of myeloperoxidase [8] acting as a retinal macrophage. Hypochlorite ion (-OCl), a myeloperoxidase product may oxidize the heteroatoms (N-, S-, O-) in phenothiazines [9] similar to its action proposed to cause drug induced hepatotoxicity and neutropenia. These ocular redox reactions differ among individuals, given the polymorphic expression of the oxidative enzymes- myeloperoxidase, glutathione-S-transferase, and gamma-glutamylcysteine synthetase [9]

It has been suggested that CPZ and TRZ are hydroxylated by retinal P450 myeloperoxidase (MPO) at position 7 of the phenothiazine ring, forming reactive quinones resulting in hepatotoxicity and neutropenia [10]. This can be extrapolated to the retinopathy seen with CPZ, TRZ and FPZ metabolized by retinal P450 myeloperoxidase to an electrophile, quinoneimine [11], implicated as the causative factor for the IDRs.

A common hypothesis widely used to explain the idiosyncratic drug-induced liver injury is the adaptive immune response hypothesis. Inflammation, induced by bacterial or viral pattern recognition molecules, or by underlying disease conditions, has been shown to increase the toxic responses to CPZ. CPZ is known to cause hepatic cholestasis [12], neuroleptic malignant syndrome [13] and rhabdomyolysis [14]. As per the 'two hit hypothesis', intrinsic toxicity of chlorpromazine with an additional factor is required to cause hepatic injury [15,16]. Here the authors cotreated rats with chlorpromazine and a small dose of liposaccharide (LPS), an inflammagen. Neither LPS nor CPZ alone altered serum creatinine kinase (CK), known to be elevated in neuroleptic malignant syndrome and rhabdomyolysis but cotreatment with LPS and CPZ showed elevated CK, although the source for the rat CK was a different enzyme as compared to humans. Serum hepatic enzymes were also significantly elevated with LPS and CPZ cotreatment. The authors also noticed that most of the IDRs seen with chlorpromazine were preceded by inflammatory signs such as fever, abdominal distress and other signs associated with endotoxemia. It was concluded that inflammation is a causative factor for IDRs in chlorpromazine.

LPS and other proinflammatory cytokines are also known to down-regulate major cytochromes P450, impair phase-2 conjugating enzymes and basolateral and canalicular transporters of bile acids and organic anions [17]. One particular study found that CPZ generated an early oxidative stress, altered mitochondrial membrane potential and disorganized pericanalicular cytoskeletal F-actin distribution in human HepaRG cells [18] with inhibition of taurocholic acid (TA) efflux. A subsequent study [19] to confirmed that pro-inflammatory cytokines, interleukin-6(IL-6) and interleukin-1B (IL-1B) induced CPZ hepatotoxicity. It was found that IL-1B strongly induced C-reactive protein (CRP) mRNA and protein levels. Further IL-1B induced mRNA and protein levels of IL-8 [20]. Also, it was noticed that CPZ-treated cells had an increased accumulation of intracellular vesicles, in the presence or absence of the cytokines. These vesicles are required19 for lipid metabolism and phospholipidosis- ADFP, PLIN4, SCD1, LPIN1, THRSP. They were also found to dowregulate CYP3A4 and CYP1A2, major CYP450 enzymes, along with CYP2D6.

It is known that the gram positive bacterial outer membrane component-lipoteichoic acid (LTA) and gram-negative membrane-lipopolysaccharide (LPS) activate Toll-like receptors (TLR) to induce inflammation [21]. In a primary study done on rat hepatocytes [22], hepatotoxicity with chlorpromazine was markedly augmented when pretreated with the pro-inflammatory cytokine-tumor necrosis factor a (TNF-a), or bacterial endotoxins-LPS or LTA. LPS or LTA activate TLRs 4 and 2 respectively, leading to the recruitment of the first adaptor protein, TIRAP (toll interleukin 1 receptor domain containing adaptor protein) to the intracellular domain of TLRs [23]. TIRAP has been shown to attenuate the production of inflammatory cytokines in response to TLR4 or TLR2 [24]. However, in the study, TIRAP mediated the alteration of hepatic detoxification genes by LTA, but was not involved in mediating the effects of LPS on these genes.

TIRAP-dependent TLR-signaling pathway involves mitogen activated protein (MAP)-kinase and c Jun N-terminal kinase (JNK). It has been suggested [22] that transient activation of JNK helps in cell survival, whereas sustained activation leads to apoptosis. Augmentation of CPZ toxicity by TNFa in primary mouse hepatocytes was associated with sustained activation of JNK [22-24]. Additionally, TNFa mediated increase in CPZ hepatotoxicity was attenuated by a JNK inhibitor.

A subsequent study [25] proved that LPS or LTA treatment led to sustained activation of JNK and release of TNFa, ultimately causing CPZ induced hepatotoxicity. TIRAP played an important role in regulating the effects of LPS or LTA. However, the molecular mechanism was not explored further in the study. CYP2D6 catalyzes CPZ metabolism and CYP1A2 [26] does so but to a lesser extent. Although LPS is known to downregulate the gene expression of several CYP isoforms in mice, the effects of LPS or LTA on CYP2D6 require further study.

Clozapine

A study was done to test the hypothesis that polymorphisms of MPO and CYP2D6 are associated with clozapine induced agranulocytosis [27]. A single base substitution (G-463A) in the MPO promotor region has been linked to reduce transcription rate, resulting in decreased MPO activity [28]. However, no statistically significant different MPO genotype frequency could be observed between the 31 clozapine induced agranulocytosis subjects and the controls. The authors concluded that there could be a need for more samples of clozapine patients to conclude. Also, it is important to note that patients with congenital MPO-deficiency exhibit long-life eosinophilia [29], suggesting that clozapine may be causing its IDR due to a similar pathophysiology [30].

Another study was done to find whether the reactive metabolite of clozapine is cytotoxic towards polymorphonuclear (PMN) and mononuclear leukocytes (MNL). The study used horseradish peroxidase (HSP) and hydrogen peroxide (H2O2) [31] in order to release the reactive metabolites. However, clozapine and its stable metabolites: desmethylclozapine and clozapine N-oxide show no cytotoxicity towards PMNs and MNLs. It is known that myeloperoxidase, a major enzyme in PMNs can activate clozapine to a reactive cation and then to a nitrenium ion, an unstable product [32] making it difficult to be isolated. As per the danger hypothesis, it is believed that the nitrenium ion binds to a macromolecule leading to agranulocytosis [33]. Hence, an in vitro assay was developed to generate the unstable metabolite in situ coupled with assessment of PMN and MNL viability and characterization of the metabolite. Interestingly, the glutathione (GSH) levels fell, required for the detoxification mechanism. The results matched with the postulation that nitrenium ion is cytotoxic to PMN and MNL at therapeutic doses of clozapine.

Additionally, a review analyzed the potential mechanism of clozapine-induced agranulocytosis with coadministration of clozapine and proton pump inhibitors (PPI) [34]. It is known that clozapine can also develop the side effect of gastroesophageal reflux disease (GERD), the most common gastrointestinal complication associated with this drug [34]. PPIs, when usually coadministered with clozapine have a large drug-drug interaction in terms of hematological adverse reactions [35] demonstrated by a study [36] on 26 clozapine recipients with hematological adverse events, of which 96% were found to had taken PPI or ranitidine. Omeprazole, a PPI, is a known agonist of the aryl hydorcarbon receptor (AHR) [36] that can increase the expression of the mRNA responsible for the synthesis of FM-O3 enzyme [37]. Flavin-containing monooxygenase (FM-O3) enzyme is present in leukocytes, known to assist in the generation of the nitrenium ion, a reactive oxygen species generated after further metabolism of clozapine metabolites- N-desmethylclozapine and clozapine N-oxide. This study appears to provide a strong explanation; however, recent studies were not confirmatory [37]. Moreover, long term administration of AHR agonists on the FM-O3 has not been investigated. Further, PPIs are known to inhibit or induce CYP450 isoforms [38], and particularly shown to induce CYP1A2 [39]. with the severity of the impact dependent of the polymorphism of CYP. Induction of CYP isoforms would eventually lead to increased clozapine metabolites. Based on an in vitro trial, clozapine was found to inhibit CYP2C19 metabolism [40], demonstrated by the increase in clozapine concentration by more than 2 fold in poor CYP2C19 metabolizers [41] suggesting that poor metabolizers are more prone to PPI-clozapine interactions.

MEDICATION	GENOME SITE	PROPOSED MECHANISM	CLINICAL EFFECT
Fluoxetine	Oxidative damage	Free radical formation and impaired antioxidant defense	Hepato-toxicity
Sertraline	MPT induction by ANT CYP2C19	Mitochondrial impairment Poor metabolizers	Hepato-toxicity
Escitalopram	SNP rs6311	Serotonin transporter polymorphisms	Memory loss
Amitryptiline	CYP2D6 and CYP2C19	CYP2D6-1 has higher risk of adverse events	
Venlafaxine	CYP2D6 polymorphism CYP450 polymorphism	loss of function allele	Suicidal tendencies

Trazodone	CYP2D6 polymorphisms	m-CPP toxicity	Hepato-toxicity

Table 3: Idiosyncratic Drug Reactions to antidepressant medications.

MPT= Mitochondrial pore transporter; ANT= Adenine nucleotide translocator; JNK= C-Jun terminal kinase; CYP= Cytochrome; SNP= Single nucleotide polymorphisms.

Although case reports do not provide a significant sample size, it is important to discuss a report [42] on monozygotic twins, diagnosed with paranoid schizophrenia and being treated with clozapine. Both suffered agranulocytosis and were found to be heterozygotes for C3435T and G2677T. It has been proposed that clozapine metabolites act as substrates or inhibitors to multidrug resistance gene I product (MDR1) of C3435T and G2677T polymorphisms [43] These genes alter P-glycoprotein, a MDR I product that functions as a membrane protein exporting xenobiotics from cells. The authors suggested that the polymorphisms may have caused an additive functional loss in P-gp action, resulting in toxic metabolites and, hence, the agranulocytosis.

Antidepressants

Fluoxetine

A study [44] was designed to investigate the effect of one month of exposure to fluoxetine on oxidative stress markers in rat livers and to determine the toxic effect of fluoxetine. The transaminase levels were found to be elevated suggestive of hepatotoxicity. Although no changes were seen in the concentrations of fluoride ion, that are indicative of oxidative stress, the levels of thiobarbituric acid reactive substances (TBARS), carbonyl groups and the levels of uric acid were significantly increased. To explain the outcomes of no difference in the fluoride ion concentrations, it was suggested that fluoxetine contains a very stable carbon-fluorine bond in the trifluoromethyl (CF-) group. Uric acid is known to be a strong scavenger of oxidative stress molecules or free radicals [45], although some studies have shown uric acid to be a pro-oxidant [46]. Carbonyl groups are final protein oxidation products [47] and TBARS is an indicator of lipid peroxidation. The study concluded the presence of free radical generation and impaired antioxidant defense system as causes of this IDR.

Sertraline

A study [48] was done to evaluate the toxic effects of sertraline on rat hepatocytes. A set of mitochondrial assays were performed including oxygen consumption, mitochondrial membrane potential, and measurements of individual complex activities in isolated mitochondria. After measuring for cellular adenosine triphosphate (ATP) content of hepatocytes, ATP depletion was clearly observed in a time- and concentration- dependent manner. Prolonged or worsening ATP depletion is known to be an indication of irreversible mitochondrial damage and cell death [49]. It is known that the mechanisms of drug-induced mitochondrial dysfunction include uncoupling of electron transport from ATP synthesis, inhibition of mitochondrial complexes, opening of the mitochondrial permeability transition (MPT) pore, and inhibition of mitochondrial deoxyribonucleic acid (DNA) polymerase [50]. MPT pore is a protein pore formed by structural molecules such as voltage-dependent anion channel, adenine nucleotide translocase (ANT) and cyclophilin D (CyPD) [51].

Being interested in identifying the target responsible for MPT induction, two MPT blockers were used, BA and cyclosporine A, that target different components of MPT pore. Mitochondrial swelling was prevented by the ANT inhibitor-BA but not by the cyclophilin D inhibitor-cyclosporine A. Further BA attenuated both ATP depletion and lactate dehydrogenase (LDH) release, a toxicity parameter caused by sertraline, but cyclosporine A had little effect. Hence, it was concluded that ANT may be the primary target for MPT induction (per a previously established glucose-galactose assay [52] that relied on different culture media forcing the cells in a galactose media to rely on a mitochondrial oxidative phosphorylation compared to the use of glucose media). It was found that sertraline caused similar toxicity in both galactose- and glucose-media, that stresses that mitochondrial impairment may be just one of the important contributors to sertraline-induced hepatotoxicity. Also, it has been shown that poor CYP2C19 metabolizers had a higher level of sertraline than normal metabolizers [53]. Interestingly, sertraline showed inhibitory effects on mitochondrial complexes I and V.

Escitalopram

A study [54] was done in India to show an association of serotonin transporter SLC6A4 and receptor polymorphisms HTR1A and HTR2A during treatment with escitalopram in patients with major depressive disorder. The polymorphism seen with 5-HTTLPR occurs due to insertion/deletion of 44 base-pair variations that influence gene expression. It has a long L allele and a short S allele, with reports in Caucasian population showing a positive association between L allele and better response [55], although some studies failed to show such an association [56]. Four single nucleotide polymorphisms (SNPs) were selected- rs6311, rs6313, rs6295, and a 5-HTTLPR 44 base-pair insertion deletion were selected due to extensive literature on them. No significant association was found in the SNPs analyzed and the response to escitalopram. However, an adverse effect of memory loss was associated with rs6311.

Amitryptiline

Differences have been noted in nortriptyline clearance, an active metabolite of amitryptiline after genotyping for CYP2D6 and CYP2C19 [57]. On analyzing CYP2D6, carriers of a dysfunctional allele (2D6-1) had a higher risk for adverse events than cases with functional alleles (2D6-2). It was also hypothesized that slower CYP2C19 metabolizers (2C19-1) who are also faster metabolizers regarding CYP2D6 (2D6-2) should display the lowest risk of adverse events.

Trazodone

Another study [58] showed CYP2D6 inhibitors diminished the cytotoxicity of trazodone and its metabolite m-chlorophenyl piperazine (m-CPP) toward isolated hepatocytes. It was proposed that polymorphisms in human CYP2D6 enzyme might contribute

to the idiosyncratic nature of the hepatic injury induced by trazodone [58,59].

Venlafaxine

In a particular study [60], DNA was extracted from deceased patients who committed suicide after venlafaxine treatment. The goal was to study cytochrome P450 genotyping, given the observations that polymorphic variations in the CYP450 genotype could be used to adjust doses in treatment resistant patients [61]. In one patient, loss of function of CYP2D6 was noted. Another patient's test revealed CYP2D6 polymorphism with decreased enzyme activity. Test on a family with three members on venlafaxine treatment revealed the loss-of function CYP P450 allele in all the family members.

Nefazodone is an antidepressant agent that was temporarily withdrawn in 1988 due to being linked with liver failure. This outcome was attributed to its inhibitory effects on the mitochondrial respiratory complexes I and IV and depolarization of the mitochondrial membrane [50].

Ethnic Differences

HLA subtypes in clozapine induced agranulocytosis

Various studies done on Ashkenazi Jewish and non-Jewish Caucasian populations with clozapine-induced agranulocytosis found associations with HLA-B38, DRB1*0402, DQA1*0301 and DQB1 *0302 in 33Jewish Caucasians, and with HLA DR*02, DQB1*0502 and DQA1*0102 in 19 non-Jewish Caucasian patients [62-64]. Also, HLA-B35 seemed to have a protective effect in the non-Jewish population [65].

Interestingly, there was a higher frequency of HLA-DQB*0201 in Caucasian patients with agranulocytosis as this haplotype has been recognized in Jewish Caucasians [64] as well, establishing it as a common genetic marker for these distinct ethnic groups. However, in another study [65] involving 103 patients with a history of clozapine-induced agranulocytosis, no significant association was noted among HLA-A, -B, -C, -DR, -DQ, number of neutrophil-specific alloantigens and susceptibility to clozapine-induced agranulocytosis. The results were later questioned with regards to statistical methodology.

Further, a study [66] on non-Jewish Caucasian subjects with schizophrenia concluded HLA class I and II antigens two locus haptotype associations- Cw7-B18 and Cw7-B39, two-locus haplotype- DRB5*0201, DRB4*000 and three-locus haplotype associations HLA-Cw7-B18-DRB5*000, HLA-Cw7-B39-DRB5*000 and HLA-Cw7-B44-DRB5*000 to be additional targets for agranulocytosis. Another study [67] in a Finnish population concluded to have demonstrated an association between HLA-A1 and a good response to clozapine. Other research [68] did not support such a significant association. However, a weak association was found between HLA-B16 and agranulocytosis. This association has been reported in Ashkenazi Jews as well as in native American patients [62,69].

HLA genotyping of monozygotic schizophrenic twins with clozapine agranulocytosis revealed different HLA alleles with HLA-A28 and 26 , HLA-B 49 and 63 , and DR 2 (vs.16), 12 and 52 present in the two subjects [70].Heat shock proteins have been also suspected to play a role in IDRs [71].The authors found HSP70-1 A and HSP70-2 9.0-kb variants to be in linkage association with HLA-B38-DR4 haplotype in Jewish patients, and with the HLA-DR2 haplotype in non-Jewish patients. An excess number of HSP70-1 C and HSP70-2 8.5-kb variants were seen in the control group. Therefore, these were concluded to be protective against agranulocytosis [72].

Investigations [73] of TNF-[alpha] variants (polymorphisms and microsatellites) in 12 Jewish and 21 non-Jewish schizophrenic and schizoaffective patients with clozapine induced agranulocytosis revealed higher frequencies of TNF-[alpha] microsatellites d3, b4 and b5 in both ethnic groups. The NQO2 gene encodes an enzyme that catalyzes the two-electron reduction of quinones and quinoid compounds and uses dihydronicotinamide riboside as an electron donor [74]. The NQO2 gene was studied in 98 Jewish schizophrenic and schizoaffective clozapine-treated patients, 18 of whom had developed agranulocytosis [75]. Of these 18 patients, 11 were positive for HLA-B38. The promoter region was genotyped intensively: ten polymorphisms in the coding regions, in intron 1, and in the promoter region were identified. Association of polymorphisms in intron 1 suggested that this site might be a susceptibility locus of agranulocytosis.

Whole exome sequencing done in a Finnish study [76] focused on three genes nominally associated with clozapine agranulocytosis: PPFIA4 (protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin),a4), ubiquitin-specific peptidase 4 (USP43) and actinin -a-1 (ACTN1). PPFIA4 belongs to liprin, a protein family that interacts with leukocyte common antigen-related receptor protein tyrosine phosphatase F and plays a role in maintaining cell-cell adhesion [77]. The SNP of the PPFIA4 rs903365 is recognized as a potential weak promoter/enhancer region. USP 43 processes poly-ubiquitin precursors and ubiquitinated proteins to interact with the 14-3-3 family of proteins [78] that function in cell growth, differentiation, survival and apoptosis [79]. The SNP of USP 43 rs12450515 alters transcription factor binding. SNP rs3742897 is located in an intronic region of ACTN1, expressed throughout the body especially by monocytes, neutrophils and T-cells. ACTN1 has a role in T-cell migration in the adaptive immune response [80].

However, the authors concluded that no significant associations could be found suggesting an extremely complex genetic etiology, or that etiologic gene variants were not captured due to small sample size.

DRUG CLOZAPINE	ETHNICITY	HLA GENOTYPING
Study I	Ashkenazi Caucasian Jews	HLA B38,DRB1*0402,DQA-1*0301,DQB1*0302
	Non-Jewish Caucasians	DR*02,DQB1*0502,DQA1*0102 B35was protective

Study II	Non-Jewish Caucasians	Cw7-B18 and Cw7-B39 DRB5*0501 and DRB4*000 Cw7-B18-DRB5*000,Cw7-B39-DRB5*000,Cw7-B44-DRB5*000
Study III	Ashkenazi Jews and Native Americans	HLA-B16
Study IV	Finnish population	HLA-A1

Table 4: Agranulocytosis factors/Ethnic differences.

Conclusion

The available data on psychotropic IDRs suggests a very broad range of mechanisms, with some more data supported than others. It is fair to conclude that the evidence regarding the pathophysiologies of IDRs is yet to be fully understood. Nevertheless, genetic factors are an important commonality. At this time a good foundation has been laid for further investigations using advanced technologies. The following is a brief discussion of these exciting approaches.

Future Directions

Homology modeling is a methodology to predict protein structure based on the general observation that proteins with similar sequences have similar structures [81]. Based on the homology model, the 3D structure of HLA molecules can be identified with more than 9000 HLA alleles identified thus far [82]. Although this approach predicts a reasonably accurate model of the allele of interest, there are a large number of HLA allelic variations with many polymorphisms.

Amari et al. developed a homology modeling approach (a HLA modeler) which provides a greater degree of detail. A local database of 3D structures of HLA molecules is used. Ultimately, recognition of the antigen peptide binding site structure (which is highly conserved in alleles) is achieved as it binds the drug molecule. The HLA modeler can then reproduce the site corresponding closely to the crystal structure. A scientific vector language (svl) is used in a software system MOE (molecular operating environment) and a segment matching algorithm is used for modeling and optimizing by PFROSST field.

Docking simulations are used to study biomolecular interactions and mechanisms and are also applied to structure-based drug design. Hence, this is useful for evaluating the binding affinity of a drug at the antigenic peptide binding site of the relevant HLA molecule by predicting bound conformations and free energies of binding for small molecule ligands to proteins. It is expected that docking simulations can predict potential idiosyncratic drug reactions in the early stage of drug development.

One such docking program described in the literature is ASE Dock, based on the shape of the molecule such as concavity of the protein and the ligand. Impressively, almost 80% of structures reconstruct within experimental error.

Quantitative systems pharmacology (QSP) modeling is a computer modeling technique that incorporates known biology and physiology in order to understand in vitro data. For example, in drug induced liver injury, a QSP approach describes physiological processes such as bile acid homeostasis and disruption, mitochondrial activity and toxicity, reactive metabolite generation and disposition, oxidative stress, inflammatory mediation by the immune system and overall hepatocyte cell cycle. It is a common tool for assessing drug efficacy but has recently been adopted for exploration of potential drug toxicity [83].

Given the substantial morbidity and mortality associated with psychotropic IDRs, and the ever-expanding pharmacopeia, such systematic approaches as the above, and others yet to be developed that allow for reasonable prediction of IDRs, are welcomed and much needed.

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