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Targeting neurotransmitter-mediated inflammatory mechanisms of psychiatric drugs to mitigate the double burden of multimorbidity and polypharmacy

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ABSTRACT

The increased incidence of multimorbidities and polypharmacy is a major concern, particularly in the growing aging population. While polypharmacy can be beneficial, in many cases it can be more harmful than no treatment, especially in individuals suffering from psychiatric disorders, who have elevated risks of multimorbidity and polypharmacy. Age-related chronic inflammation and immunopathologies might contribute to these increased risks in this population, but the optimal clinical management of drug-drug interactions and the neuro-immune mechanisms that are involved warrants further investigation. Given that neurotransmitter systems, which psychiatric medications predominantly act on, can influence the development of inflammation and the regulation of immune function, it is important to better understand these interactions to develop more successful strategies to manage these comorbidities and complicated polypharmacy. I propose that expanding upon research in translationally relevant human *in vitro* models, in tandem with other preclinical models, is critical to defining the neurotransmitter-mediated mechanisms by which psychiatric drugs alter immune function. This will define more precisely the interactions of psychiatric drugs and other immunomodulatory drugs, used in combination, enabling identification of novel targets to be translated into more efficacious diagnostic, preventive, and therapeutic interventions. This interdisciplinary approach will aid in better precision polypharmacy for combating adverse events associated with multimorbidity and polypharmacy in the future.

1. Polypharmacy and psychiatric comorbidities

It is a major triumph that advances in public health and modern medicine have enabled people to live and even thrive while afflicted with one or more chronic diseases. However, many human diseases are resistant to treatment from any single drug, so concurrent use of multiple medications, termed polypharmacy, is often the treatment standard. In many circumstances, polypharmacy in patients with complex medical problems is an appropriate and necessary therapeutic approach that can improve clinical outcomes, quality of life and life expectancy. However, it is also associated with major concerns regarding patient safety and efficacy of treatment, including harmful drug interactions, medication non-adherence, and an increased risk of hospitalization and mortality (Maher et al., 2014; Hohl et al., 2001; Khezrian et al., 2020). In addition, polypharmacy has the potential to cause a 'prescribing cascade', in which a drug administered to a patient causes adverse symptoms that can be misinterpreted as a new condition. This can result in a new medication being prescribed and increases risks to the patient as well as healthcare costs (Cahir et al., 2010; Stewart et al., 2017; Shah and Hajjar, 2012; Chiatti et al., 2012; Rochon and Gurwitz, 2017). Moreover, the high rates of geriatric disease, long-term side effects from hospitalization, and "long-haul" syndrome during the COVID-19 pandemic will most certainly exacerbate complications and escalate problematic polypharmacy (Rahman et al., 2020; McKeigue et al., 2021; Elbeddini et al., 2021).

Currently, the most effective method for mitigating problematic polypharmacy remains in having systemic controls that continuously monitor and revise prescription to ensure that only necessary drugs are administered at the lowest effective dose. Still, one of the challenges of treating multimorbidity with this approach is that therapeutic prescriptions are largely based on single-disease guidelines. Investigating the effectiveness and safety of medications is mainly achieved through randomized controlled trials, where patients with multiple chronic conditions are often excluded (Tinetti et al., 2004; Nobili et al., 2011; Boyd et al., 2005; Molokhia and Majeed, 2017). This creates a number of issues as these are the patients that are seen increasingly in clinical practice; and who are most likely to be affected by adverse drug interactions. In

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particular, these issues affect a large proportion of individuals suffering from psychiatric disorders, who have an elevated risk of multimorbidity as well as a shorter life expectancy with an increased occurrence of fatal intoxication and polypharmacy (Reuss et al., 2021; Kukreja et al., 2013; Dennis et al., 2020). This double burden of multimorbidity and prescription drugs is an increasing problem in the growing aging population (Nobili et al., 2011; de Lima et al., 2020; Ersoy and Engin, 2018). However, these issues are not exclusive to the elderly as associations between mental illness, chronic diseases and polypharmacy have been found to occur at every age, showing a lifelong progression (Menditto et al., 2019). Not only is a new outlook on this research needed to better understand the relationship between polypharmacy and health outcomes as we age, but also to identify and develop effective prevention strategies for younger individuals.

2. Age-associated inflammation and immunopathologies as risk factors for psychiatric multimorbidity and polypharmacy

In recent years, psychoneuroimmunology research has provided compelling evidence suggesting that inflammation plays a critical role in psychiatric disorders, including schizophrenia, depression, PTSD, and bipolar disorder (Potvin et al., 2008; Miller and Raison, 2016; Baumeister et al., 2014), and that inflammatory effects vary significantly between them. This highlights the potential for inflammatory mediators as suitable biomarkers and therapeutic targets (Yuan et al., 2019). Immune-mediated changes shown to be associated with psychiatric disorders include increased levels of inflammatory markers including interleukin (IL)-6 and C-reactive protein (CRP) in blood and CSF, hypothalamic-pituitary-adrenal axis hyperactivity, activation of microglia, the primary innate immune cells of the central nervous system (CNS), and a variety of alterations in the function of circulating immune cells (Söderlund et al., 2009; Beumer et al., 2012a, 2012b; Müller et al., 2012; Dowlati et al., 2010; Martinez et al., 2012; Passos et al., 2015; Berk et al., 2011; Bayer et al., 1999; Horowitz et al., 2013). Some of these same immunologic changes are also associated with increased multimorbidity (Stepanova et al., 2015; Fabbri et al., 2015), as well as higher daily drug consumption (Ersoy and Engin, 2018). Further, low-grade inflammation is associated with aging, chronic infections, and autoimmune disease, which are all risk factors for developing psychiatric disorders.

Dysregulation of the immune system is a hallmark of aging, resulting from defects in the initiation and resolution of immune responses and chronic low-grade inflammation (Franceschi and Campisi, 2014; Franceschi et al., 2007; Montecino-Rodriguez et al., 2013). Age-related effects are seen in both adaptive and innate immunity in both the periphery and the CNS (Frasca et al., 2011; Kilpatrick et al., 2008; Pang et al., 2011; Rea et al., 2018). In the CNS, there are age-related changes in microglia, including defects in phagocytosis, aberrant epigenetic modifications, and disruptions in neuronal-microglial communication (Matt and Johnson, 2016; Cho et al., 2015; Conde and Streit, 2006; Damani et al., 2011; Dilger and Johnson, 2008). My prior research with Dr. Johnson demonstrated that aged mice have decreased DNA methylation of IL-1β in primary microglia basally or following systemic lipopolysaccharide (LPS). This is associated with increased IL-1β mRNA, intracellular IL-1β production, as well as prolonged sickness behavior (Matt et al., 2016). Additionally, comorbid chronic infections and inflammatory diseases can exacerbate age-associated immune dysfunction (Koch et al., 2007; Naggie, 2017; Goronzy and Weyand, 2012), neuronal damage and altered neurotransmission linked to depression, anxiety and schizophrenia (Weissenborn et al., 2006; Adinolfi et al., 2015; Loftis et al., 2008; Watkins and Treisman, 2012; Bhadra et al., 2013). Further, long-term effects of medications used to treat infections and inflammatory diseases can themselves induce depressive and psychotic symptoms (Raison et al., 2005; Kaestner et al., 2012; Mollan et al., 2014). As dysregulation of the immune system may mediate, at least in part, the development of psychiatric disorders, age-related changes in microglial function are likely to contribute to the accumulation of psychiatric disease burden and subsequent polypharmacy (Deleidi et al., 2015; Godbout and Johnson, 2009).

One of the most studied chronic infections associated with accelerated aging and neurological impairments is HIV. Age-related comorbidities are becoming increasingly prevalent in people living with HIV (Deeks, 2009, 2011) including several neuropsychiatric disorders (Cahill and Valadéz, 2013; Milanini et al., 2017; Brandt et al., 2016) which contribute to cognitive decline and neuropathology (Havlik et al., 2011; Arseniou et al., 2014). Despite the frequent co-administration of antiretroviral therapy (ART) and psychiatric drugs in this vulnerable population, little information exists regarding the optimal clinical management of drug-drug interactions. Many psychiatric and antiretroviral drugs affect neurotransmitter systems that are associated with the progression of both HIV and psychiatric disorders (Nolan and Gaskill, 2018; Launay et al., 1989; Scheller et al., 2010). Therefore, drug-associated changes in these neurotransmitters could be a more common mechanism contributing to the adverse effects in HIV-infected individuals (Matt and Gaskill, 2019a). For example, my recent study in Dr. Gaskill's lab showed that pharmacologic dopamine levels can alter the efficacy of the antiretroviral Maraviroc in primary human macrophages (Matt SM et al., 2021). Although yet to be examined, drug-induced changes in neurotransmitter levels could alter medication efficacy in other age-related chronic inflammatory conditions presenting with increased risk for neuropsychiatric comorbidities, such as rheumatoid arthritis (van Onna and Boonen, 2016) and multiple sclerosis (Sanai et al., 2016).

3. Immunomodulatory effects of psychiatric drugs: current and future experimental strategies

Several studies have examined the immunomodulatory effects of psychiatric drugs such as antidepressants and antipsychotics. *In vivo*, many studies show significant decreases in peripheral inflammatory markers after starting a psychiatric medication regime. However, there are differences across studies in the specific inflammatory markers affected, and these changes may not be specific or relevant to the brain environment, as other studies show no change in some of these markers despite significant improvements in depression severity or psychosis (Hannestad et al., 2011; Hiles et al., 2012; Strawbridge et al., 2015; Dahl et al., 2014; Tourjman et al., 2013; Alcocer-Gómez et al., 2014; Mondelli et al., 2015; Cattaneo et al., 2013). Many questions remain about whether inflammation that accompanies psychiatric disease is a cause or a consequence of the disease itself. And just as importantly, it is not clear whether a reduction of inflammatory markers following effective pharmacotherapies is mediated by the drugs or the reduction of psychiatric symptoms.

To address these questions from the basic science perspective, the immunomodulatory effects of antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOis), as well as typical and atypical antipsychotics, have all been examined *in vitro* in primary human peripheral immune cells, as well as in animal models (Baker et al., 2020). For antidepressants, the results are relatively straightforward although contradictory. Some antidepressants, such as clomipramine and fluoxetine, more consistently decrease inflammatory cytokines while others (mirtazapine and venlafaxine) increase cytokine levels (Xia et al., 1996; Maes et al., 1999, 2005; Lin et al., 2000; Kubera et al., 2002, 2004; Diamond et al., 2006; Carvalho et al., 2008; Himmerich et al., 2010; Krause et al., 2012; Munzer et al., 2013; Tsai et al., 2014; Waiskopf et al., 2014; Kawasaki et al., 1999). Relative to the studies on antidepressants, the *in vitro* studies on antipsychotics are more complex, showing a large array of outcomes (Rudolf et al., 2002; Szuster-Ciesielska et al., 2004; Himmerich et al., 2011; Krause et al., 2013; Bleeker et al., 1997; Leykin et al., 1997; Hinze-Selch et al., 1998; Moots et al., 1999; Song et al., 2000; Chen et al., 2011, 2013). It is surprising, considering the prevalence of psychiatric polypharmacy and the number of older individuals taking these medications, that to my knowledge there are no studies examining

primary peripheral immune cells from older individuals. Future experiments are necessary to explore the utility of these cells to account for age-specific inflammatory effects.

Many studies posit a link between psychiatric disorders and peripheral inflammation, but we still need to better understand the role of CNS inflammation in these disorders. A handful of studies have examined changes in microglia, using rodent primary microglia and microglial cell lines (Dubovický et al., 2014; Hashioka et al., 2007; Su et al., 2015; Tynan et al., 2012), demonstrating that antidepressants such as venlafaxine and fluoxetine have anti-inflammatory effects. However, the immunological differences between rodents and humans (Mestas and Hughes, 2004; Zschaler et al., 2014) indicate that the use of human microglia and microglial models are also needed to confirm these effects. Perhaps more importantly, only few studies have investigated discrete inflammatory effects of individual drugs relative to drug combinations. Overall, the immunomodulatory impact of psychiatric drug combinations has shown additive inflammatory and anti-inflammatory effects on cytokine production (Bortolasci et al., 2018; Petersein et al., 2015), but warrant further investigation.

Currently, differences between *in vivo* and *in vitro* studies, as well as interexperimental variation in sample types and methodological approaches make the specific immunomodulatory impact of psychiatric drugs difficult to discern. There is also a rich pharmacological profile of psychiatric drugs to consider, which is quite different not only between classes (i.e., TCAs versus SSRIs) but also at the level of individual drugs within a class (citalopram versus sertraline). In particular, the differences in both pharmacodynamics and pharmacokinetics of these drugs in combination with other drugs and disease states may produce unpredictable major side effects that may not be related to interactions with the immune system. Acknowledging and accommodating these issues should guide the development of future studies examining these interactions, but we should also consider how the indirect, downstream effects of psychiatric drugs influence immunity. More attention needs to be given to how changes in the neurotransmitters themselves are influencing inflammation, to effectively study and eventually help to explain the direct effects of psychiatric drugs alone and in combination on the immune system.

Advances in our rapidly evolving mechanistic understanding of cytokine production and secretion in the CNS (Reyes et al., 1999; Sébire et al., 1993; Choi et al., 2014; Peferoen et al., 2014) suggest numerous pathways by which cytokines influence the synthesis and signaling of neurotransmitters such as serotonin (Chou et al., 2016; Malynn et al., 2013), dopamine (Felger and Miller, 2012; Felger et al., 2015), and glutamate (Ida et al., 2008; Haroon et al., 2014). Unfortunately, we know far less about the mechanisms by which these neurotransmitters influence inflammatory signaling. A wide variety of immune cells including lymphocytes, monocytes, macrophages, and microglia, express surface receptors and other machinery for neurotransmitters like noradrenaline, acetylcholine, dopamine, serotonin, and glutamate, allowing them to respond directly to these signals in the brain but also the periphery (Besser et al., 2005; Ganor et al., 2003; Levite et al., 2001; Pocock and Kettenmann, 2007; Gaskill et al., 2012; Matt and Gaskill, 2019b). In human macrophages, we have shown that dopamine can increase macrophage cytokine production (Nolan et al., 2018), and increase NF-κB activity and prime the NLRP3 inflammasome in what may be a dopamine receptor subtype-specific manner (Nolan et al., 2020). Intriguingly, it has recently been found that neurotransmitters such as dopamine and serotonin can themselves act as epigenetic modifiers, serving as donors for covalent modifications on specific residues of histone proteins (Lepack et al., 2020; Farrelly et al., 2019). It remains to be seen how these post-translational modifications occur in immune cells, but it is an exciting example of the enormous potential for neurotransmitters to influence immune function that needs to be further explored.

Although serotonin, norepinephrine, dopamine, and their metabolites have been measured successfully in some immune cell populations (Cosentino et al., 1999, 2000, 2002; Maestroni et al., 1998; Marino et al., 1999; Marcusson et al., 2000), the capacity for immune cells to release these neurotransmitters is not completely understood. But as these cells were examined after drug administration *in vivo*, it is unclear if psychiatric drugs would directly affect these cells or if additional neurotransmitter release from other cell types is needed to mediate these effects. The latter situation is likely as studies examining the effects of drugs of abuse on inflammation have found that acute treatment of mice with either cocaine or methamphetamine significantly increases IL-1β in the CNS *in vivo*, but this effect was not seen *ex vivo* in microglia isolated from these animals (Cearley et al., 2011; Frank et al., 2016). These studies suggest that drug-induced increases in neurotransmitters such as dopamine, and not the drugs themselves, are at least partially mediating the increase in IL-1β. To address this, I propose efforts to develop translationally relevant, human *in vitro* models to directly study neurotransmitter and psychiatric drug-specific cellular and molecular mechanisms (see Fig. 1). This will help to identify specific novel processes and pathways that mediate the effects of neurotransmitters/psychiatric drugs on the immune system. Further, this can drive further basic and translational studies that may provide potential connections that can be targeted to ameliorate the immunological side-effects of psychiatric polypharmacy.

4. Human-relevant cell model systems for understanding basic immunopharmacology of neurotransmitters and psychiatric drugs

The development of iPSCs (Takahashi et al., 2007) offers one attractive way to develop clearly defined systems to investigate the basic mechanisms of psychiatric drugs on neurotransmitter-mediated immune function. Already, models have been established to study psychiatric disorders such as depression, schizophrenia, and bipolar disorder (Akkouh et al., 2020; Ni et al., 2020; Brennand et al., 2011; Mertens et al., 2015; Soliman et al., 2017; Reis de Assis et al., 2021), by reprogramming cells from individuals with psychiatric disorders into iPSC-derived neurons and astrocytes. Applying these models to the generation of iPSC-microglia and other immune cell populations will be an important future direction to investigate the direct effects of neurotransmitters on their function and to monitor their response to distinct combinations of drugs. To precisely interrogate the neurotransmitter-mediated versus psychiatric drug-mediated effects, use of iPSC co- and tri-culture models could be used. These multi-cell systems would provide cell–cell interactions that mimic *in vivo* environments (Goudriaan et al., 2014; van Deijk et al., 2017; Ryan et al., 2020). Perhaps more importantly, these systems would enable comparison of the distinct impact of psychiatric drugs in a human *in vitro* system where neurotransmitter release is known to be evoked (Lin et al., 2021) rather than in *in vitro* monocultures of immune cells where little to no neurotransmitter release would be present. Additionally, the development of iPSC-derived 3D systems, organoids, has shown tremendous potential, as these systems can more closely recapitulate the architecture and physiology of human organs (Kim et al., 2020). For the CNS, different strategies are being used to generate organoids representing specific regions (Yoon et al., 2019; Smits et al., 2019; Muguruma, 2018). Some of these systems innately develop astrocytes and microglia (Ormel et al., 2018; Velasco et al., 2019) and model neurovasculature, allowing investigation of the permeability of CNS therapeutics (Bergmann et al., 2018). Increasingly, brain organoids are being used not only to study neurological disorders in the more classic sense (Wang, 2018), but also to model neuroimmunopathologies such as neuroHIV (dos Reis et al., 2020) and MS (James et al., 2021).

Building a foundation of clearly defined immunomodulatory effects of psychiatric drugs in these co-culture and 3D models will foster a more mechanistically precise method to study large numbers of drugs alone and in combination. Close collaboration with clinicians will be essential to direct us towards the most used psychiatric drug combinations, or those that produce the most significant adverse effects. Indeed, basic researchers and clinicians could work together to design experiments to examine the immunomodulatory outcomes of specific drug treatments

Fig. 1. Dr. Stephanie Matt. Dr. Matt first discovered her passion for science as an undergraduate at the University of Delaware, working with Dr. Tania Roth identifying epigenetic mechanisms in the rat brain associated with early-life caregiving experiences. She then went on to complete her Ph.D. at the University of Illinois at Urbana-Champaign in the Integrative Immunology and Behavior Lab of Dr. Rodney Johnson. Her graduate work focused on exploring epigenetic regulation of microglial activity in mice, as well as evaluating potential pharmacological and dietary interventions that act as epigenetic modifiers that could ameliorate chronic age-related neuroinflammation. During this time, she also began her active membership in the Psychoneuroimmunology Research Society, attending her first annual meeting in 2014. She is currently pursuing postdoctoral training in the lab of Dr. Peter Gaskill at Drexel University, where her work focuses on dopamine-mediated changes in inflammation and HIV infection in human macrophages and microglia. Her work suggests that dopamine-mediated changes in inflammation will be important to effectively tailor antiretroviral regimens to HIV-infected individuals who abuse drugs, and more broadly additional studies are critical to fully understanding the impact of many commonly used dopaminergic and other neurotransmitter-mediated therapeutics. In the future, she aims to combine sophisticated human cell/tissue culture models with advanced molecular and high-throughput imaging technologies to investigate ways in which neurotransmitters and drugs that modulate neurotransmitter levels alone and in combination affect myeloid cell inflammatory function. Ultimately, her goals are to continue to mentor and support future generations of neuroimmunologists by establishing an independent research program using a multidisciplinary approach to investigate the role of neurotransmitters in mediating regulation of inflammation. The hope is to aid in the development of new therapeutic strategies that may be important for fostering better management of comorbidities and reducing cognitive deficits and neurodegenerative disease as we age.

that are surprising or problematic in a clinical setting. These cell models could also be utilized in high-content screening, a high-throughput imaging approach using automated microscopy and image analysis platforms that enables visualization and quantification by capturing many cellular features on a large scale (Li and Xia, 2019). This powerful research tool enables rapid analysis of large numbers of different conditions, ideal for testing different drug doses and combinations. Although it is primarily utilized within the pharmaceutical industry, it is gaining traction in academia, including in the Gaskill Lab (Matt SM et al., 2021; Nolan et al., 2020). Combining all these systems and tools could establish a unique bi-directional pipeline, in which clinical experience, questions and results drive basic research into the nuanced immune responses to neurotransmitters and drugs. The results of this basic research can then inform further clinical trials and treatment strategies.

As polypharmacy and immune dysfunction are particularly prevalent in the aging population, one of the primary challenges in using these models will be to develop an appropriate way to study human aging. Many iPSC-based aging models require additional stressors such as ROS or excitotoxic glutamate concentrations to elicit disease-specific phenotypes, while others use gene mutation/telomerase inhibition models (Nguyen et al., 2011; Seibler et al., 2011; Miller et al., 2013; Vera et al., 2016), which do not recapitulate the manifestations of biological aging. As an alternative, strategies to directly convert cells from one lineage to another, thus bypassing the rejuvenating embryonic state, are being employed to maintain the age-associated features of donor cells (Chambers and Studer, 2011). Protocols have been established for the direct conversion of many cell types, including blood cell lineages, hepatocytes and neurons (Huang et al., 2014; Laiosa et al., 2006; Vierbuchen et al., 2010). As microglia-specific direct conversion protocols and adaption of these cells into organoids advance, this will provide a unique opportunity to understand how the aging process impacts them and how neurotransmitters and psychiatric drugs would influence their immunophenotype. This is important as aberrant neurotransmitter changes mediated by psychiatric medications can be caused by age-related neurophysiological changes such as declines in neuronal density and neurotransmitter synthesis (Kratz and Diefenbacher, 2019). What is also very exciting about direct conversion is the preservation of cellular epigenetic profiles (Huh et al., 2016; Tang et al., 2017) that are erased in pluripotent cells (Lo Sardo et al., 2017). As several psychiatric drugs have been shown to modify the epigenome (Boks et al., 2012), this technology could also be useful in the identification of specific genetic/epigenetic signatures involved in drug-responses (Cazaly et al., 2019).

Another factor to consider is that while research into psychiatric drugs often focuses on the CNS, these drugs could produce neurotransmitter-mediated immune effects in nearly every organ. And neurotransmitters don't just act in the CNS, they are heterogeneously distributed throughout the body, so the CNS impact of drugs may differ substantially from their peripheral effects. To address this, systematic analyses of the similarity and dissimilarity of drug-induced inflammation across tissues in different disease models would be invaluable. This would better inform us on the predominantly systemic drug-induced concentrations of cytokines that are currently examined in clinical studies and provide a resource that could be translated into the clinic for more personalized drug dosing recommendations based on existing inflammatory comorbidities and current medication. In patients or in animals *in vivo*, these types of studies would be complex and costly. But with the technology of organoids that can be grown for almost every organ and incorporate nearly all cell types from that organ system, as well as multi-organoids-on-a-chip systems (Yin et al., 2021; Picollet-D'hahan et al., 2021), these analyses will become more feasible. In tandem, these systems, in particular models for the liver (Underhill and Khetani, 2017), blood–brain barrier (BBB) (Bergmann et al., 2018), and gut microbiome (Li et al., 2019) can be utilized to better understand potential drug-drug kinetic and metabolomic changes, which are the major concerns for polypharmacy in older adults (Malki and Pearson, 2020). While these models are not a substitute for *in vivo* modeling and human trials, as

among other limitations they are prone to lose phenotypic characteristics related to factors such as gender, obesity, and trauma, they could provide the initial data needed to refine tissue-specific inflammation-related targets and drug-drug interactions. This could vastly reduce the cost and complexity of the higher-level *in vivo* studies.

5. A combinatorial approach for linking advances in basic psychoneuroimmunology to their potential relevance for psychiatric polypharmacy

Polypharmacy is not going to disappear anytime soon. Rather it is likely to increase, as populations age and the number of people with multiple long-term conditions increases. It is also not realistic to rely on the development of new "magic bullet" drugs to combat these comorbidities. A more reasonable tactic will be to adopt a "precision polypharmacy" approach that includes risk identification and implementation of personalized strategies that minimize medications in vulnerable populations. This type of precision medicine would rely on multiple technology-based solutions as well as interdisciplinary teamwork for linking advances in basic psychoneuroimmunology to their potential relevance for psychiatric diseases. Specific clinical questions about neuro- and immunopathologies or particular drug combinations will push psychoneuroimmunology labs to use human *in vitro* models, animal systems, postmortem human samples and *in vivo* imaging techniques to define specific neurotransmitter and psychiatric drug-induced cellular and molecular mechanisms. The results of these studies will then be translated into more efficacious diagnostic, preventive, and therapeutic interventions (Fig. 2).

Importantly, the amelioration of psychiatric symptoms due to immunotherapy does not always correlate with reductions in inflammatory biomarkers (Raison et al., 2013). Indeed, many questions remain about the connections between specific inflammatory effects and different psychiatric diseases. This highlights the importance of integrating these emerging experimental and analytic pipelines with existing biomarkers and other resources to assemble a comprehensive precision polypharmacy approach. For example, pharmacogenetic testing is increasingly used to identify genetic biomarkers that predict individual sensitivity to particular drugs, and pharmacogenetic polymorphisms may represent independent risk factors for older adults with polypharmacy (Finkelstein et al., 2016). With the increasing availability of 'big data' repositories that link health data and genomics, there is enormous potential to evaluate the real-world clinical impact of multiple drugs with multiple genetic variant interactions. These data sets can be mined for information and used in predictive modeling along with other advanced

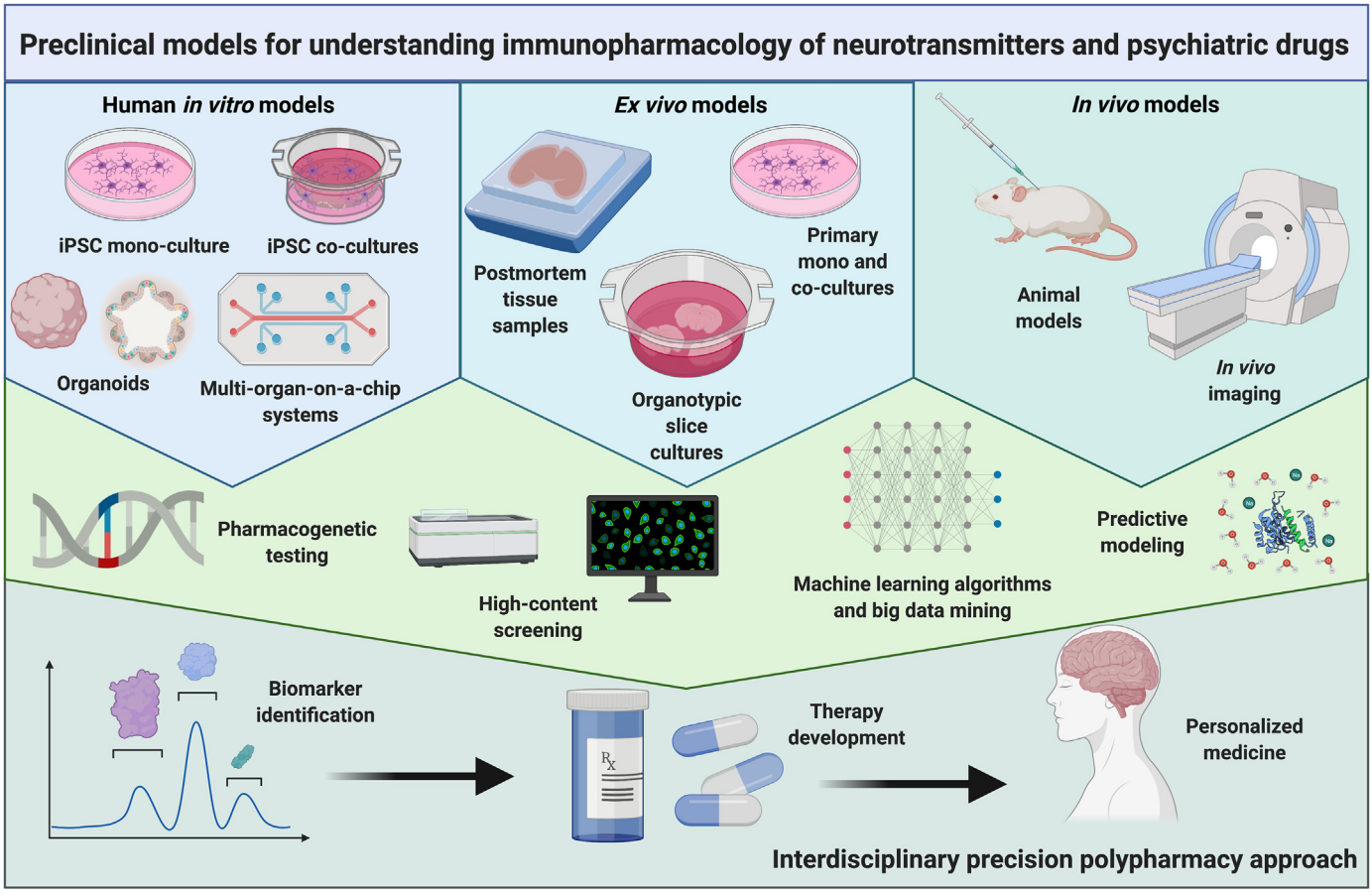

Fig. 2. An interdisciplinary "precision polypharmacy" approach for linking advances in basic psychoneuroimmunology to their potential relevance for psychiatric diseases. I propose a precision strategy that relies on multiple preclinical models from psychoneuroimmunology labs to define specific neurotransmitter and psychiatric drug-induced cellular and molecular mechanisms. These include human *in vitro* models such as iPSC mono- and co-culture systems and organoids, *ex vivo* primary cell/tissue and postmortem human samples and *in vivo* animal systems and human imaging techniques. Parameters warranting further investigation include but are not limited to understanding neurotransmitter release in immune cells, neurotransmitter receptor signaling involvement in the immune response, and delineating neurotransmitter-mediated inflammation from inflammation mediated by psychiatric drugs alone and in combination. The integration of these strategies with high-content screening platforms, pharmacogenetic testing, as well as predictive modeling and mining of other high-dimensional proteomic and metabolomic analyses can be leveraged to help identify new candidate biomarkers. This will then be translated into more efficacious diagnostic, preventive, and therapeutic interventions for combating adverse events associated with multimorbidity and polypharmacy in the future. Created with BioRender.com.

analytics applications and be combined with our preclinical techniques in the lab. This will enable more precise evaluations of novel mechanisms/pathways to identify clinically important interactions that can be incorporated into powerful decision support tools in the clinic.

6. Conclusion

While the evidence for immunomodulation by psychiatric drugs is apparent, the extensive crosstalk between immune cells and the neurotransmitters that these drugs act on in disease and multi-disease states is complex. A more comprehensive research approach is needed to define novel mechanisms and disruptions more precisely in neuroimmune communication driven by psychiatric drugs used alone and in combination, as well as with other immunomodulatory drugs. One way to address this is with new, translationally relevant human model systems. Much of the research in the growing psychoneuroimmunology field bridges clinical and basic research, making it well-situated to take advantage of these technologies and redefine "precision polypharmacy" by integrating the results from these new human systems with existing clinical practices, trials, and clinical data repositories. Identifying the dysregulation of specific molecular inflammatory pathways, age-related phenotypes, and genetic/epigenetic signatures, due to psychiatric polypharmacy will allow for identification of novel targets for therapeutic intervention. Further mechanistic understanding of the common polypharmacy regimens that exist when taking drugs such as regimens for individuals suffering from depression who also have neuropathic pain, HIV, or MS, could enhance treatment efficacy and discovery. One could imagine that anti-inflammatory agents, selective neurotransmitter agonists/antagonists, or even antibody-based treatments could be developed or repurposed as potential therapies for both neuro- and immunopathologies. This could also involve the development of multi-drug single-tablet regimens that are being used for ART, combining drugs that synergistically improve pharmacokinetics or block each other's unwanted actions to provide more beneficial effects for vulnerable patient subgroups like older adults with psychiatric polypharmacy. This will lead to widespread health gains and prevention strategies for combating adverse events associated with multimorbidity and polypharmacy in the future.

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Declaration of competing interest

The author of this manuscript declares that they have no conflicts of interest either directly or indirectly related to the content of this manuscript.

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