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Percutaneous transport of psychotropic agents

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ABSTRACT

Treatment rates for mental and substance abuse disorders are low, particularly in low and middle-income countries (LMICs), where treatment gaps of more than 90% have been documented [1]. Psychiatric disorders are particularly debilitating. One of the ways of improving pharmacotherapy of patients suffering from schizophrenia, depression, bipolar disorder and other psychiatric conditions is through the use of transdermal drug delivery systems (TDDS). The advantages of TDDS include avoidance of first-pass effect, the possibility of providing sustained release and improving patient compliance. There are several techniques available for facilitating the percutaneous transport of medications across the skin. These include prodrugs, chemical penetration enhancers, transfersomes and proniosomes. This review discusses advances made in the transdermal delivery of psychotropic medications.

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1. Introduction

Mental disorders affect a large percentage of the global population and lead to significant morbidity, mortality, and disability [2]. In 2010, mental and substance disorders accounted for 7.4% of global disability-adjusted life years (DALYs) and 22.9% of global years lived with disability (YLDs), making them the fifth leading cause of DALYs and the leading cause of YLDs [3]. In 2013, nearly 1 in 5 adults (an estimated 43.8 million people) aged 18 or older (18.5%) had a mental illness in the USA and 4.2% had a serious mental illness (SMI) [4]. The main psychiatric disorders are schizophrenia [5], depressive disorders [6,7], attention deficit/hyperactivity disorder [8], unipolar and bipolar affective disorders [9] and anxiety disorders [10-12].

1.1. Schizophrenia

It has been suggested that schizophrenia is probably the most severe type of psychiatric disorder [5]. The disease affects approximately 21million people globally [13] and is the third most disabling illness of the central nervous system worldwide with a global cost of 23.7 million disability-adjusted life years (DALYs) [5]. In the United States, 0.7% of the US population, or roughly 2 million Americans suffer from the disease [14]. Schizophrenia is characterized by positive symptoms (hallucinations and delusions), negative symptoms (socially withdrawn behavior), cognitive dysfunction, and affective dysregulation [15]. Other symptoms of this disease include formal thought disorder and disorganized or abnormal motor behavior [5]. Patients suffering from schizophrenia display cognitive deficits which affect processing speed, attention, working memory, verbal learning, visual memory, and executive functioning [16]. The etiopathogenesis of this complex, highly heritable and polygenic neuropsychiatric disease is yet to be ascertained [17] but a vertiginous array of abnormalities of varied neurotransmitters, cell types, brain regions and epidemiologic associations is thought to be implicated [18].

Most studies seek to integrate the roles of genetic liability, neurodevelopmental anomalies, aberrant synapse function, and environmental factors such as neonatal infections and substance use, yet the manner in which these distinct factors coalesce into the neurobiology of schizophrenia remains unclear [18]. It has been recently reported that several microRNA (miRNA), including microRNA 7 (miR-7), are expressed differentially in the postmortem prefrontal cortex of schizophrenia patients in comparison with healthy controls [19]. An increasing body of evidence has also found increased oxidative stress in patients suffering from schizophrenia, including in subjects who have never taken antipsychotic drugs [18]. Autoimmune mechanism is also thought to be involved in the pathogenesis of schizophrenia [17].

1.2. Major depressive disorders

Major depressive disorder (MDD) is a complex mental disorder with the following symptoms -persistent and pervasive low mood, including low self-esteem, loss of interest or pleasure, and feelings of personal worthlessness [20]. There is still a lack of a clear understanding of the neuropathological changes associated with this illness [21]. However, the monoamine hypothesis of depression continues to dominate the field [21]. According to this postulate, there is an imbalance in monoaminergic neurotransmission which is causally related to the clinical symptoms of depression [21].

The lifetime prevalence of MDD is around 15%, which makes it one of the most prevalent mental disorders [20]. Increasing evidence from behavioral and neuroimaging studies has linked MDD to major disruptions in all reward related processes, including reward anticipation, motivation and outcome [22]. The disturbed reward processing in MDD patients is linked to disconnections within mesolimbic striatum-based reward circuitry [22]. Lower functional connectivity (FC) has been shown in the ventral tegmental area (VTA), striatum, and ventromedial prefrontal cortex (VMPFC), and weakened responsiveness to repetitive transcranial magnetic stimulation treatment of the dorsomedial prefrontal cortex (DMPFC) has been observed in MDD patients [22]. Neuroimaging studies into adult MDD have revealed dysfunction in frontal regions including medial, orbital, dorsolateral (dlPFC) and ventrolateral prefrontal cortex (vlPFC) as well as the anterior cingulate cortex (ACC) [7].

1.3. Persistent depressive disorder

Persistent depressive disorder (PDD) or dysthymic disorder (DD) tends to have milder symptoms and a chronic course compared to MDD, but with similar functional impairment [23]. This condition is characterized by persistent sad and/or irritable mood for a period lasting one year or longer [7]. DD may best be considered as being at the lower end of a depressive spectrum with less severe but more persistent symptoms [7]. The change of label from DD to PDD is a reflection of this dimensional approach [7]. The utility for pharmacotherapy for PDD is often debated, as the impaired mood, interpersonal dysfunction, and anhedonia often seen in PDD patients are frequently perceived as characterological deficits, not as symptoms [23].

1.4. Attention Deficit/Hyperactivity Disorder

Attention Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental condition characterized by inattention, hyperactivity and impulsivity [8]. It is postulated that there is dysregulation of fronto-striatal circuits and the neurotransmitters involved in these pathways in ADHD patients [8]. In particular, emerging data implicate altered dopamine signaling [8]. There are three subtypes of ADHD, one marked by predominantly inattentive symptoms (ADHD-I), the second by hyperactivity and impulsiveness (ADHD-H), and the third displays a combination of inattentiveness and hyperactivity (ADHD-C) [24].

ADHD occurs in 6–8% of children and 2–3% of adults [25]. Although the exact causes of ADHD are unknown, the interplay between primary biological and secondary environmental risk factors plays an important role in this disorder [24]. A variety of genetic-environmental interactions have been implicated in ADHD, particularly those involving dopamine, such as DAT1, a dopamine transporter gene [24]. In addition, ADHD imaging studies showed cortical changes, including reductions in size and functional activity in the prefrontal cortex, as well as abnormalities in dopamine transport [24]. There are also reports showing that the noradrenergic system is involved in ADHD [26]. Neuropsychological and