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The many different faces of major depression: It is time for personalized medicine

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ABSTRACT

First line antidepressants are the so-called SSRIs (selective serotonin reuptake inhibitors), e.g. fluvoxamine, fluoxetine, sertraline, paroxetine and escitalopram. Unfortunately, these drugs mostly do not provide full symptom relief and have a slow onset of action. Therefore other antidepressants are also being prescribed that inhibit the reuptake of norepinephrine (e.g. reboxetine, desipramine) or the reuptake of both serotonin (5-HT) and norepinephrine (e.g. venlafaxine, duloxetine, milnacipran). Nevertheless, many patients encounter residual symptoms such as impaired pleasure, impaired motivation, and lack of energy. It is hypothesized that an impaired brain reward system may underlie these residual symptoms. In agreement, there is some evidence that reuptake inhibitors of both norepinephrine and dopamine (e.g. methylphenidate, bupropion, nomifensine) affect these residual symptoms. In the pipeline are new drugs that block all three monoamine transporters for the reuptake of 5-HT, norepinephrine and dopamine, the so-called triple reuptake inhibitors (TRI). The working mechanisms of the above-mentioned antidepressants are discussed, and it is speculated whether depressed patients with different symptoms, sometimes even opposite ones due to atypical or melancholic features, can be matched with the different drug treatments available. In other words, is personalized medicine for major depression an option in the near future?

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Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; CRF, corticotropin-releasing factor; HPA, hypothalamus-pituitary-adrenal; WHO, World Health Organization; DSM-5, Diagnostic and Statistical Manual of Mental Disorders 5; MOA, monoamine oxidase; VMAT, vesicular monoamine transporter; COMT, catechol-O-methyltransferase; TCA, tricyclic antidepressant; SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; NRI, norepinephrine reuptake inhibitor; DNRI, dopamine–norepinephrine reuptake inhibitor; TRI, triple reuptake inhibitor; PFC, prefrontal cortex; NAc, nucleus accumbens; LC, locus coeruleus; VTA, ventral tegmental area; BNST, bed nucleus of the stria terminalis; ICSS, intracranial self-stimulation; MCP-1, monocyte chemotactic protein-1; NMDA, N-methyl-D-aspartic acid

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1. Introduction

This contribution in the Festschrift for Berend Olivier is about antidepressant drugs and personalized medicine. Major depression destroys the life of many patients and their families. It is estimated that depression increases the risk of suicide by 20 times. Depression is one of the most prevalent mental disorders, affecting about 121 million people worldwide and is among the leading causes of disability. The World Health Organization (WHO) estimates that by the year 2020, depression will be the second most common cause of disease and premature death worldwide (Murray et al., 2014), and by 2030 depression will be the leading cause of disease burden in the world (Mathers and Loncar, 2006). Furthermore, depression is one of the most common reasons that people are absent from work, or are unable to run a home.

1.1. The history of monoaminergic antidepressants

The history of antidepressants is one of serendipity. Not intended, but keen perception to link together apparently innocuous facts has lead to the first antidepressant drugs. In the 1950s a drug called iproniazid was developed for the treatment of tuberculosis. Being ineffective in treating tuberculosis, however, it was found to be effective in reducing depressive symptoms in some patients that were primarily suffering from tuberculosis or other infections/inflammations (Loomer et al., 1957). It was discovered that iproniazid worked by inhibiting the enzyme monoamine oxidase (MOA), which is located in a neuron's nerve terminals (Zeller and Barsky, 1952). The enzyme MAO is responsible for breaking down the excess release of monoamines, such as norepinephrine, dopamine and serotonin (5-HT). Thus, MAO-inhibitors (MAOIs) increase levels of synaptic monoamines in the brain. Consequently, it was postulated that major depression was associated with a decrease in synaptic activity of neural connections that employ monoamine neurotransmitters; or, in other words, reduced the levels of monoamine neurotransmitters in the brain. Interestingly, further support for this idea came, although not without controversy, from the observation that the drug reserpine produced depressive mood in patients (Kass and Brown, 1955). Reserpine irreversibly blocks the vesicular monoamine transporter (VMAT) (Henry and Scherman, 1989) and lowers monoamine levels in the brain, because free intracellular monoamines cannot be transported into the presynaptic vesicles for subsequent release into the synaptic cleft (Kopin, 1994). Although the first MAOIs were very effective, they were also problematic because of the strict diet people needed to follow to prevent toxic consequences and other side effects of the drug. Recent advancements in technology, however, may alleviate some of these safety issues for instance by administering MAO inhibitors (e.g. selegiline) transdermal (Stahl and Felker, 2008).

In 1956, the Swiss psychiatrist Ronald Kuhn tested a chlorpromazine-like product (now known as imipramine) in patients with schizophrenia. Kuhn saw in individual patients the potential of imipramine as an antidepressant, although it was not effective in schizophrenia. By the end of 1957 he had presented imipramine's positive effects on depressed mood in a larger patient cohort (Kuhn, 1957, 1958). The pharmaceutical company Ciba-Geigy brought imipramine onto the European market in the late 1950s and into the U.S. in 1960. Imipramine was the first tricyclic antidepressant (TCA). Called tricyclic because the molecular structure had three rings of atoms. Unfortunately, TCAs have many adverse side effects and are easily overdosed with possible life-threatening consequences. TCAs had become the WHO number-one recommended drug for major depression by the beginning of 1970.

Between 1958 and 1961, Julius Axelrod carried out experiments on the regulation of neurotransmitters that earned him the Nobel Prize in 1970. Axelrod discovered that monoamines in the brain are rapidly metabolized by the enzyme catechol-O-methyltransferase (COMT) in the brain (Axelrod and Tomchick, 1960). But more surprisingly Axelrod and collaborators (Axelrod et al., 1961; Herting et al., 1961) showed that radiolabeled neurotransmitter monoamines were taken up into nerve terminals, which subsequently could be blocked by cocaine (now known as a triple monoamine reupake inhibitor) (Axelrod et al., 1961; Herting et al., 1961). Axelrod's work on the synthesis, metabolism, and reuptake of neurotransmitters provided lasting insights into the mechanisms of the chemical synapse. Today these insights form the basis for using MAO-enzyme-inhibitors and reuptake-inhibitors for the treatment of Parkinson's disease (MAO-B inhibitors) and major depression (e.g. MAO-A inhibitors and SSRIs), respectively (Stahl and Felker, 2008).

The development of SSRIs has dramatically changed the landscape of psychopharma-cotherapy of major depression. The Swedish pharmaceutical company Astra marketed the first SSRI zimelidine in 1982, but it was already withdrawn in 1983, because several patients developed the Guillain–Barré syndrome. Berend Olivier is co-developer of the first SSRI antidepressant in the world; named Fevarin (fluvoxamine) that is still used for major depression and obsessive–compulsive disorders. In 1984 it appeared first on the market in Switzerland followed by other European countries in 1985 and 1986. It was only in 1988 that Prozac (fluoxetine) appeared on the market in the USA as an antidepressant. Because of Eli Lilly's very effective marketing strategy, Prozac became the number one antidepressant. Many other SSRIs followed, such as paroxetine, sertraline, citalopram and escitalopram (the *S*-enantiomer of citalopram). SSRIs have replaced tricyclic antidepressants (TCAs) as the drugs of choice in the treatment of depressive disorders, not because of their better efficacy, but because of their improved tolerability and safety (Steffens et al., 1997). In 2006, however, a meta-analysis by the FDA showed an age-related side effect of SSRIs, indicating a higher risk for suicidal behavior among adults younger than 25 years (Henry and Demotes-Mainard, 2006). In retrospect, this may have been the case in one of the two shooters of the Columbine High School massacre, who was on fluvoxamine when he committed suicide after killing 13 people. Consequently, in the USA this drug rapidly lost favor and market share, and Solvay voluntarily withdrew fluvoxamine from the US market. Thereafter, many more casualties have been reported in the media in young people (some were victims of bullying) that used SSRIs, or just had started or had stopped SSRI treatment. This is very important because undertreated mood disorders can have severe negative consequences. Since 2004, after the FDA safety warnings and widespread media coverage, SSRI antidepressant use dramatically decreased, also in young people. Simultaneously, there was an increase in suicide attempts among young people (Lu et al., 2014). Thus, this FDA warning and media coverage might have produced unintended consequences. Recently, it was published that fluoxetine should remain the antidepressant of first choice in the treatment of young depressed patients, and appeared superior to paroxetine or a TCA (Qin et al., 2014). Thus, families and doctors should carefully weigh the risks and benefits, and closely follow and monitor to help control for the risks. Patients should never suddenly stop SSRI-medication, without consulting his/her general practitioner, because this may cause severe negative withdrawal side effects. Results of a comprehensive review of pediatric trials conducted between 1988 and 2006 suggested that the benefits of SSRI medications likely outweigh the increased suicide risk in children and adolescents with major depression and anxiety disorders (Bridge et al., 2007). Recently, it has been hypothesized that the use and withdrawal of SSRIs, MAO-inhibitors and TCAs are linked to REM sleep behavior disorder (Parish, 2007). This disorder is a clinical condition characterized by violent or frightening dreams which are “acted out” by the patient. Thus, more research is needed to understand why some young people due to SSRI medication become a risk for themselves (self-directed aggression) and/or their environment (externally-directed aggression) (Bouvy and Liem, 2012).

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