Treatment Consideration and Manifest Complexity in Comorbid Neuropsychiatric Disorders

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Psychiatric disorders may co-occur in the same individual. These include, for example, substance abuse or obsessive-compulsive disorder with schizophrenia, and movement disorders or epilepsy with affective dysfunctional states. Medications may produce iatrogenic effects, for example cognitive impairments that co-occur with the residual symptoms of the primary disorder being treated. The observation of comorbid disorders in some cases may reflect diagnostic overlap. Impulsivity, impulsiveness or impulsive behaviour is implicated in a range of diagnostic conditions including substance abuse, affective disorder and obsessive-compulsive disorder. These observations suggest a need to re-evaluate established diagnostic criteria and disorder definitions, focusing instead on symptoms and symptom-profiles.

Keywords: Treatment; Symptoms; Obsessive-compulsive; Psychosis; Comorbidity; Schizophrenia; Impulsivity; Affective; Epilepsy; Substance abuse; Neuropsychiatry

INTRODUCTION

The high incidence of substance abuse disorder in psychotic and schizophrenic patients frustrates attempts at treatment (Maslin, 2003; Drake et al., 2004). The magnitude of substance abuse in schizophrenic people would appear to be of the order: nicotine > heroin > cocaine > cannabis (the prevalence of nicotine abuse > 85% is remarkable), with patients possessing a 4.6-fold greater risk of abuse of any substance and a 3.3-fold greater risk of alcohol abuse compared to controls.

Abuse potential in schizophrenia remains a recurring theme, not least in the particular vulnerability for smoking and nicotine addiction (cf., Dalack and Meador-Woodruff, 1996; Ziedonis and Trudeau, 1997; Dalack et al., 1998; 1999; Combs and Advocat, 2000; McCreadie, 2002; Mori et al., 2003; Pencer and Addington, 2003). Risk for addiction has been linked to the occupancy of dopamine (DA) D2-like receptors by neuroleptic compounds where low availability is associated with greater addictive risk. De Haan et al. (2006) investigated whether patients with relatively high D2-like receptor occupancy by neuroleptic drugs (therefore having low availability) were more prone to nicotine consumption. They found that the frequency of cigarette smoking in schizophrenic patients treated with antipsychotic medication was significantly and negatively related to the availability of striatal D2-like receptors. Results link comorbid schizophrenia and nicotine abuse to antipsychotic...
medication effects.

Barrowclough (2007) addressed the issue of alcohol and drug use by psychotic patients. Drug abuse has a prevalence estimated to be as high as 60% in this patient population; this is a formula for disastrous outcomes, with symptom exacerbations, relapse, violence and suicide. She described the Manchester Pilot Study demonstrating that psychotic patients with substance abuse benefited from a sustained psychological approach to their "dual diagnosis problem-profile" combining family motivational interviewing and cognitive behavioural therapy. Current neuropsychopharmacological approaches seek to outline the determinants of substance usage, including the neurobiological roots of etiology and the interactive complications of substance abuse in schizophrenia and other neuropsychiatric disorders (Addington and Addington, 1998; George et al., 2000; Herran et al., 2000; Haustein et al., 2002; Peterson et al., 2002; Spring et al., 2003; Els, 2004). Green (2006) provided an example of this approach. Substance abuse disorders occur commonly in schizophrenic patients showing increases in violence, hospitalisation, treatment non-compliance and overall deterioration in prognosis. Although typical antipsychotic medications appeared to be of limited value in these patients, preliminary data suggested that the atypical antipsychotics, particularly clozapine, might be helpful. Adjunctive medications, such as those that have recently been shown to be useful for the treatment of alcoholism, may also have a role in the treatment of these patients, although only naltrexone has been carefully tested in these comorbid patients. Further studies are indicated to assess the role of novel pharmacological treatment strategies for these patients (Green et al., 2002; 2003; 2004). The percent of remission attained for alcohol abuse was markedly higher for clozapine (79%) than for typical neuroleptics (33%). Clozapine may act at prefrontal cortical (PFC) sites where it affects impulsivity (Coyle, 2006; Krystal et al., 2006). The control of drug abuse by antipsychotics was shown to be of the order: clozapine > olanzapine > risperidone > typical neuroleptics. By considering the site of action of the most effective therapeutic compounds, it may be possible to begin to understand the underlying mechanisms of comorbid neuropsychiatric disorders.

SCHIZOPHRENIA SPECTRUM DISORDER COMORBIDITY

Weizman et al. (2007) outlined the comorbidity of schizophrenia and obsessive-compulsive disorder (OCD; estimated to occur in 7.8 to 25% of schizophrenic patients) focusing on clinical aspects, neurobiology and treatment. They described a five- to six-step continuum ranging from OCD alone through to schizophrenia alone with several disorder combinations and their shared features, including drug abuse, affective disturbances and suicidal behaviour (cf., Eisen et al., 1997; Kruger et al., 2000; Lysaker et al., 2000). Brain structures implicated include the PFC, and the neurotransmitters DA and serotonin may be involved. OCD precedes the diagnosis of schizophrenia and is associated with a predisposing incidence of Tourette's disorder, implying the same gene responsible for tics and OCD. Compulsive behaviours in OCD are reminiscent of stereotypical behaviours seen in animals treated with high doses of DA agonists, and it is well documented that these same high doses can cause psychoses. These observations and the therapeutic efficacy of atypical antipsychotic agents, e.g., olanzapine, suggest neuropathophysiological convergence of OCD and psychoses (Poyurovsky et al., 2000). At the same time, each is distinct as a clinical entity, emphasizing the need for better understanding of the underlying neural mechanisms.

The issue of comorbidity may have special significance in connection with OCD. For example, obsessive-compulsiveness and impulsivity co-occur in a range of neuropsychiatric states, so-called obsessive-compulsive spectrum disorders (cf., McElroy et al., 1994; Hollander and Wong, 1995; Hollander et al., 1996); both features may be observed simultaneously or sequentially (Skodol and Oldham, 1995; Stein et al., 1996). Compulsivity is characterised by exaggerated harm perception together with excessive, over-reflective responses, and difficult-to-control harm/ risk avoidance behaviours whereas impulsivity is characterised by an underestimation of harm, non-reflective responses, difficult-to-control desires and repeated attempts to obtain pleasure and/or self-gratification (Li and Chen, 2006). Impairment of the ventral PFC, innervated by serotonergic neurons (Kamali et al., 2001), was implicated in impulsivity (Raine
et al., 1998; Hoptman et al., 2002). Furthermore, measures of OCD behaviours and impulsivity have been found to be similarly affected in patients with altered serotonergic function (Coccaro, 1989; Bastani et al., 1991; Goveas et al., 2004; Cools et al., 2005). Several studies reported poor impulse control in obsessive-compulsive spectrum disorders (Hoehn-Saric and Barksdale, 1983; Lacey and Evans, 1986; Rasmussen and Eisen, 1994; McEnroy et al., 1995; Matsunaga et al., 2005). Recently, Li and Chen (2006) tested a non-clinical, healthy volunteer adolescent population through application of the Barratt Impulsivity Scale, version 11 (BIS-11, Barratt and Patton, 1983; Patton et al., 1995; see also Barratt, 1965; Someya et al., 2001), and the Maudsley Obsessive-Compulsive Inventory (MOCl, Hodgson and Rachman, 1977), and suggested the utility of describing specific aspects of obsessive-compulsiveness and impulsivity in behavioural and clinical investigations (see also Simeon et al., 1995). Their observations reinforce those of previous studies showing elevated BIS and MOCl scores in OCD and related disorders (Muller et al., 1997; Krochmalik et al., 2001; Lejoyeux et al., 2002; Martins et al., 2004).

COMORBID FEATURES OF IMPULSIVE BEHAVIOUR

Impulsivity is associated with PFC functioning (Robbins, 2005), with both the dorsolateral (Hester and Garavan, 2004) and the ventromedial PFC - orbitofrontal cortex implicated (Berlin et al., 2004). One definition of impulsivity is "... a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to oneself or others" (cf., Moeller et al., 2001). Potts et al. (2006), studying electroencephalographic (EEG) responses in 37 undergraduate students, found differential functioning pertaining to punishment sensitivity in the medial frontal cortex in individuals rated as ‘High impulsives’ vs. those rated ‘Low impulsives’. Individuals presenting with disorders such as substance abuse or attention deficit hyperactivity disorder (ADHD) showed a tendency to select short-term rewards despite potentially long-term negative consequences (Potts et al., 2006). Low socialized individuals tended to be high impulsives (Goma-i-Freixanet, 1995) and to take short-term gratification (Dikman and Allen, 2000). The medial PFC is involved in the rapid processing of monetary gains and rewards (Gehring and Willoughby, 2002), and together with the anterior cingulate is implicated in dysfunctional action-monitoring in OCD (Gehring et al., 2000). Compared with controls, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) users showed greater scores on impulsivity (Bond et al., 2004; Morgan et al., 2006). Evoked potential studies have shown that there was a greater activation in the PFC (Moeller et al., 2004) and functional magnetic resonance imaging (fMRI) studies have shown a significant correlation with impulsivity scores (BIS-11) and activation in the dorsolateral PFC (Valdes et al., 2006). Results showed high impulsivity comorbid with a number of disorders and implicate the PFC in the control of impulsivity.

Impulsivity has been described as a multidimensional construct consisting of a range of related factors presenting a challenge for diagnosis and treatment (Plutchik and van Praag, 1995; Evenden, 1999; Monterosso and Ainslie, 1999; Askenazy et al., 2003; Horn et al., 2003; Reynolds et al., 2006). Pathological gambling co-occurs with impulsivity and is linked to low platelet monoamine oxidase activity (Blanco et al., 1996), altered prolactin response to m-chlorophenylpiperazine (m-CPP) (De Caria et al., 1996), and low concentrations of 5-hydroxyindoleacetic acid in cerebrospinal fluid (Nordin and Eklund, 1999), as well as frontal lobe dysfunction (Gualtieri, 1995; Cavedini et al., 2002; Chambers et al., 2003; Navas Collado and Munoz Garcia, 2004). Several self-report studies have linked pathological gambling to impulsivity (e.g., McCormick et al., 1987; Alcock and Grace, 1988; Carlton and Manowitz, 1994; Castellani and Rugle, 1995; Specker et al., 1995; Blaszczynski et al., 1997; Potenza et al., 2003; Fuentes et al., 2006). Recently, Rodriguez-Jimenez et al. (2006) investigated impulsiveness and sustained attention variables in pathological gamblers with or without a history of childhood ADHD, using BIS-11, the stop signal task, differential reinforcement of low rates of responding and the continuous performance test. Patients expressing the pathological gambling-ADHD comorbidity showed a significantly lower capacity to delay gratification and less inhibitory
control than the pathological gambling-non-ADHD and control groups. They evidenced too significantly higher scores on the test of impulsiveness than the pathological gambling-non-ADHD and control groups. In related studies in adolescents and children, scores on the Continuous Performance Test (Thompson and Nichols, 1992) and hyperactivity (Vitacco and Rogers, 2001) were associated with impulsivity have some bearing on impairments observed in adolescents showing high impulsivity (Li et al., 2006). Fuentes et al. (2006) linked impulsivity to compulsive pathological gambling. Perhaps pathological gambling should be thought of as a manifestation of impulsivity rather than impulsivity being a feature of pathological gambling.

Generally, low levels of resting cortical arousal and/or EEG-slowing have been linked to high levels of impulsivity (Barratt, 1985; O’Gorman and Lloyd, 1987; Stenber, 1992). Reduced P3 event-related potentials, associated with a wide range of personality and substance abuse disorders (see Palomo et al., 2004; also Brady et al., 1998), have been observed in impulsive-aggressive college students (Gerstle et al., 1998; Mathias and Stanford, 1999), and impulsive-aggressive prisoners (Barratt et al., 1997). In other EEG studies high levels of impulsivity were linked to antisocial and delinquent behaviour in juveniles (Farrington, 1997; Gatzke-Kopp et al., 2002), aggressive (Scarpe and Raine, 1997) and psychopathic behaviour (Hare, 1978; Lykken, 1995), and behavioural disorders in children (Raine and Jones, 1987; Lahey et al., 1995; Dougherty et al., 2003). Low resting levels of arousal/autonomic activity were associated too with expressions of aggressive and violent behaviour (Fishbein et al., 1989; Convit et al., 1991; Drake et al., 1992; Houston and Stanford, 2001). Certainly, aggressiveness and impulsivity are characteristics not easily separated, neither in their low neurophysiological arousal levels nor as behavioural constructs. College students selected for self-reported high impulsivity status showed low resting heart rates and a greater reactivity during an initial arousal challenge (Mathias and Stanford, 2003). Impulsive-aggressive individuals appeared to combine low resting arousal with higher physiology reactivity. Recently, Houston and Stanford (2005) compared two groups: Impulsive, high on BIS-11 but reporting no impulsive aggressive behaviour, and Non-aggressive control, within the normal range on BIS-11, for EEG at rest and during photic stimulation. Consistently lower frontal delta and theta activity was observed in the Impulsive group and personality assessment indicated significantly greater hostility and lifetime history of aggression in these individuals; these differences were independent of photic stimulation and underlined the comorbid status of impulsivity with disorders comprising aggressive behaviour and personality disturbances.

Impulsivity has been implicated in bipolar disorder (American Psychiatric Association, Task Force on DSM-IV) and contributes to several complications of the disorder, such as substance abuse (Allen et al., 1998; Moeller et al., 2001; Swann et al., 2004), borderline personality (Dougherty et al., 1999; Soloff et al., 2003), psychopathy (Brent et al., 1994; Hare et al., 1999), clinical depression (Corruble et al., 1999; 2003) and suicidal behaviour (Kashden et al., 1993; Fawcett et al., 1997; Maser et al., 2002; Swann et al., 2005). Raust et al. (2006) found high impulsivity to be highly associated with impairments in certain cognitive tasks, e.g., working memory, in suicidal patients (see also, Horesh, 2001; Keilp et al., 2001; Mann, 2003). Bipolar disorder consists of two important features: the impulsivity observed in the manic phase of the disorder, i.e., state impulsivity, and the stable impulsivity that may extend across mood states, i.e., trait impulsivity. Euthymic bipolar patients express higher levels of trait impulsivity than healthy individuals (Swann et al., 2001) but do not differ from bipolar patients (Swann et al., 2003). Peluso et al. (2006) recently compared levels of impulsivity (assessed with BIS) among depressed bipolar, depressed unipolar, euthymic bipolar, euthymic unipolar patients and healthy controls. They found that the stable trait impulsivity was not only higher than healthy controls in the bipolar patients (depressed and euthymic) but also in the unipolar patients (depressed and euthymic). Barratt and Patton (1983) presented the notion that impulsivity resulted from the neurophysiological inability to conform behaviour to its context or consequences. The fundamental utility of this notion is suggested from not only the presence of impulsivity-aggression comorbidity in personality disorders (Dolan et al., 2002) but also
as distinctive features of borderline personality disorder (Links et al., 1999) and antisocial personality disorder (Lish et al., 1996).

Impulsivity co-occurs with a wide range of comorbidity. It has been suggested that impulsivity-aggression together with other features, such as novelty seeking (Cloninger et al., 1993; Cloninger, 1999), present an action-continuum along the spectrum of personality and/or affective disorders (Widiger, 1991; 2005; Ekselius et al., 1994; Ball et al., 1997; Fossati et al., 2000; 2001; 2003; 2006; Ball, 2001). Accordingly, measures of impulsivity, aggression and novelty-seeking formed a part of the principle component that clustered all Cluster B personality disorders (Fossati et al., 2006). In related work, the concept of 'self-destructiveness' has been presented as an important component of affective personality, that expresses itself in a wide range of factors signifying ill health, e.g., stress, Type A behaviour, sleep problems, maladaptive coping strategies, aches and pains, etc. (Bood et al., 2004; Karlsson and Archer, 2007a,b; Archer et al., unpublished). In a recent study, three hundred high school pupils were examined using several self-report questionnaires, including the Positive And Negative Affect Schedule (PANAS), Stress-Energy, Optimism, the Uppsala Sleep Inventory, Locus of Control and the Temperament Character Inventory (Karlsson, Amcoff, Hamström, Jansson and Archer, unpublished data). In addition to scoring high on several predictors of ill health, it was found that the individuals presenting the "Self-destructive" type of affective personality expressed marked differences in Temperament and Character compared with individuals presenting the "Self-fulfilling" type of affective personality (see Table I).

The results present a remarkably straightforward relationship between type of affective personality and response scores on Temperament and Character, as well as a penchant for individuals' application of either an internal or external locus of control for events, situations, incidents, etc. "Self-fulfilling" individuals expressed significantly less temperment than "High affective" and "Self-destructive" individuals but significantly more character than "Low affective" and "Self-destructive" individu-

<table>
<thead>
<tr>
<th>Affective personality</th>
<th>Self-fulfilling</th>
<th>Low affective</th>
<th>High affective</th>
<th>Self-destructive</th>
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<tbody>
<tr>
<td>TemperamentA</td>
<td>14.26 ± 2.91</td>
<td>15.27 ± 2.81</td>
<td>15.58 ± 2.78*</td>
<td>16.63 ± 2.98*</td>
</tr>
<tr>
<td>F(0.330) = 10.33, p &lt; 0.0001</td>
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<tr>
<td>CharacterB</td>
<td>19.44 ± 3.73</td>
<td>16.99 ± 3.91*</td>
<td>17.85 ± 3.96</td>
<td>15.54 ± 3.76*</td>
</tr>
<tr>
<td>F(0.300) = 16.20, p &lt; 0.0001</td>
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<tr>
<td>External locus of controlC</td>
<td>7.11 ± 2.15</td>
<td>7.25 ± 2.56</td>
<td>9.21 ± 2.33</td>
<td>14.49 ± 2.32**</td>
</tr>
<tr>
<td>F(0.314) = 9.07, p &lt; 0.0001</td>
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<tr>
<td>Internal locus of controlC</td>
<td>12.71 ± 2.37</td>
<td>12.41 ± 2.59</td>
<td>12.65 ± 2.88</td>
<td>12.02 ± 2.46</td>
</tr>
<tr>
<td>F(0.317) = 1.3, p &gt; 0.26</td>
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</table>

\* sumsmed scores from the ‘Novelty-seeking’, ‘Harm avoidance’ and ‘Reward dependence’ factors.  
\*B sumsmed scores from the ‘Self-directedness’, ‘Cooperativeness’ and ‘Persistence’ factors.  
\*p < 0.01, vs the “Self-fulfilling” group, \*p < 0.01, vs “Low affective” group, Bonferroni’s test.  
\*C External/Internal locus of control, derived according to the procedure outlined previously (Archer et al., submitted).
als. Concurrently, "Self-destructive" individuals expressed markedly greater external locus of control (in fact, by slightly more than a factor of 2) than the "Self-fulfilling" and "Low affective" individuals. The concept, 'locus of control' (internal/external) defines individuals' own expectancies regarding the extent to which they control their own destinies on the basis of their own behaviour and characteristics (cf., Rotter, 1966; Millet and Sandberg, 2003; Millet, 2005). Thus, those presenting an 'internal locus of control' assume that outcomes are due to their own ability, skills, efforts, and/or personal characteristics whereas those individuals presenting an 'external locus of control' assume that outcomes are due to external forces, such as luck, chance, fate and/or other powerful forces. Although no significant differences between types of affective personality with regard to internal locus of control emerged, there was a tendency for the "Self-fulfilling" individuals to score highest on this factor (see Table I).

Linear regression analysis permits the examination of the extent to which positive and negative affect may be predicted from data derived from personality characteristics: Temperament, Character, External locus of control and Internal locus of control, whereby the former provided the dependent variables and the latter the independent variables. The results of the analysis, presented in Table II indicated that Positive affect could be predicted significantly from Character, Temperament and External locus of control, with the latter two being negative predictors. Conversely, it was indicated that Negative affect could be predicted significantly from Temperament, External locus of control and Character. Results provide some insight into the variables contributing to "self-destructiveness". Overall this section has shown that many results implicate impulsivity as a comorbid condition with a number of neuropsychiatric disorders.

**TREATMENT CONSIDERATIONS IN SEVERE PSYCHIATRIC DISORDER**

Patients suffering from a somatic pathology who have comorbid depression that goes untreated have a high prevalence of negative outcomes (Lobo et al., 2007). Of the 709 psychiatric patients from the

<table>
<thead>
<tr>
<th>Positive affect</th>
<th>Standardised β (Standardized weights) values from linear regression with Positive affect and Negative affect, respectively, as dependent variables, and Temperament, Character, External locus of control as independent variables.</th>
</tr>
</thead>
<tbody>
<tr>
<td>F(4,294) = 25.94, p &lt; 0.0001, adjusted R² = 0.251</td>
<td>Predicting variables</td>
</tr>
<tr>
<td>Temperament</td>
<td>-0.147*</td>
</tr>
<tr>
<td>Character</td>
<td>0.387*</td>
</tr>
<tr>
<td>External locus of control</td>
<td>-0.142*</td>
</tr>
<tr>
<td>Internal locus of control</td>
<td>0.090 NS</td>
</tr>
<tr>
<td>Negative affect</td>
<td>F(4,294) = 16.26, p &lt; 0.0001, adjusted R² = 0.170</td>
</tr>
<tr>
<td>Predicting variables</td>
<td>Standardised Beta (β)</td>
</tr>
<tr>
<td>Temperament</td>
<td>0.313*</td>
</tr>
<tr>
<td>Character</td>
<td>-0.155*</td>
</tr>
<tr>
<td>External locus of control</td>
<td>0.170*</td>
</tr>
<tr>
<td>Internal locus of control</td>
<td>0.026 NS</td>
</tr>
</tbody>
</table>

*p < 0.01. NS = not significant
Zaragossa, Spain sample (70.2% of the original hospitalised sample, 70 depressive cases and 172 healthy controls), patients fulfilling inclusion and exclusion criteria, most presented complex, severe physical conditions and several medical diagnoses. The estimated prevalence rate of depression was 19.8%. In the follow-up investigations (completed in two thirds of the sample), 35.2% of the index group and only 13.6% of the controls were rated as depressed ($p < 0.001$); additionally, 74.1% of the depression group but only 40.9% of the control group presented a "poor outcome" [depression or mortality ($p < 0.001$)]. The study confirmed that the prevalence of depressive comorbidity in hospitalised medical patients is considerable and is associated with a negative outcome. Depression increases the use of medical services and decreases quality of life. The purpose of these and other multicentre studies was to design intervention treatment strategies to improve negative outcome (see also Lobo et al., 2005).

Co-morbidity between epilepsy and affective disorders has been observed. A relationship between these disorders is supported by the use of electroconvulsive therapy (ECT; producing generalized seizures) in the treatment of depression and mania and by the use of several anticonvulsive agents for the treatment of bipolar disorder (Bolwig, 2007). Patients afflicted by seizure disorders show depressive features (cf., Kanner and Palac, 2000; Kanner and Balabanov, 2002), and from this viewpoint of treatment there seems to be commonality (Albertson et al., 1984; Robertson, 1987). The interactive role of noradrenergic and serotonergic systems, well-established in affective states (Archer et al., 1986; Quednow et al., 2004), is implicated in the associations between epilepsy and affective disorders (Jobe et al., 1999). Identification of common neurocircuitry associated with epilepsy and depression awaits further study.

Prepulse inhibition (PPI) assesses a pre-attentive process of sensorimotor gating (cf., Geyer, 2006). Deficits were seen in schizophrenic patients and in animal models of schizophrenic symptoms, e.g., neonatal ventricle hippocampal lesions, acute glutamate N-methyl-D-aspartate (NMDA) receptor antagonists, transgenic mice with glutamatergic or other abnormalities, corticotrophin releasing factor administration, etc. However, PPI deficits have been observed in other neuropsychiatric disorders: OCD, Tourette's syndrome, Huntington's disease, schizotypy, bipolar mania, panic disorder, Asperger's syndrome, 22q deletion syndrome, Lewy body dementia, Fragile X syndrome and under some conditions ADHD and post-traumatic stress disorder. Consequently, it may be concluded that PPI deficits cut across diagnostic categories.

Neurocognitive disruptions contribute both etiological and treatment complexity in comorbid neuropsychiatric illness. For example, incentive learning is mediated through the non-declarative memory systems and may rely on the striatum or medial PFC depending on the task (Knowlton et al., 1996; Beninger, 2006). These two regions are affected differentially by typical and atypical antipsychotics. This has been shown in studies of expression of the immediate early gene c-fos. Typicals increased c-fos expression in the striatum and atypical increased c-fos expression in the medial PFC (Robertson and Fibiger, 1992; Wirtshafer and Asin, 2003). These findings suggested the hypothesis that performance of schizophrenic patients on tasks differentially relying on the striatum or the medial PFC would be differentially affected by typical vs. atypical medications (Pacquet et al., 2004). Beninger et al. (2003) tested the cognitive abilities of schizophrenic patients treated with either typicals or the atypicals clozapine, olanzapine or risperidone. The cognitive tests included: probabilistic classification learning (PCL), a test of implicit memory requiring intact striatal functioning (Knowlton et al., 1996) and the Iowa Gambling Task (IGT) or theory of mind tasks requiring intact medial PFC functioning (Fletcher et al., 1995; Bechara et al., 1997). Patients treated with typicals were impaired on the PCL but not the IGT whereas the group treated with atypicals was impaired on the IGT but not the PCL. On the theory of mind task, clozapine- and olanzapine-treated patients performed as controls whereas those treated with typical neuroleptics or risperidone were impaired, implying an interactive effect of medication with psychiatric disorder (Beninger, 2006). Typical and atypical antipsychotics differed in the types of cognitive performance they affected; furthermore, members of the atypical class varied in their effects on cognition. These results suggested that the comorbid cognitive impairments observed in schizophrenia may be in part iatrogenic, adding
further complexities to the disorder (Harvey et al., 2001; Karila et al., 2007).

Molina (2007) presented results from a series of imaging studies on structural and functional aspects of schizophrenic brain (Molina et al., 2002; 2003; 2005b). Using positron emission tomography (PET) and fMRI techniques they found that risperidone induced an increase in visual area activity at rest and a significant increase in grey matter volume in the occipital and parietal areas after two years. Clozapine induced a symptom improvement-associated increase in occipital activity accompanied by a decrease in basal ganglia and frontal activity and, after two years, significant increases in grey matter volume in the frontal, occipital and parietal regions. Olanzapine induced a substantial improvement of positive symptoms associated with increased occipital metabolism. Several other structural and functional changes following long-term treatment with atypical antipsychotics were described. Results prompt the interesting insight that even structural abnormalities in the disorder may be reversible to some extent.

The frequent observation of substance abuse in schizophrenia raises questions about treatment (Albanese et al., 1994; O'Brien et al., 2004; Sacco et al., 2005). Substance abuse disorders occur commonly in schizophrenic patients and this comorbidity is associated with increases in violence, hospitalisation, treatment non-compliance and overall deterioration in prognosis. Green (2006) showed that typical antipsychotic agents had a bad prognosis for substance abuse whereas clozapine reduced smoking. The percent remission attainment on alcohol abuse was markedly higher for clozapine (79%) than for typical neuroleptics (33%). Abuse control was shown to be of the order: clozapine > olanzapine > risperidone > typical neuroleptics. Clozapine may lead to more effective treatment by influencing both limbic and striatal systems but the relevant sites of action remain a mystery.

Youdim and co-workers (2006) reviewed the therapeutic profiles of drug candidates that are designed to express a diversity of pharmacological properties and multiplicity of target sites in their actions against the symptoms of neurodegenerative disorders. For example, ladostigil (Weinstock et al., 2000a,b; Sterling et al., 2002; Youdim and Buccafusco, 2005) combines selective monoamine oxidase B (MAO-B) inhibition with cholinesterase (ChE) inhibitory activity to provide a pharmacophore-neuroprotective effect and a procholinergic propensity as well as an iron chelator moiety. Ladostigil (TV3326) [(N-propargyl-(3R) aminodan-5yl)-ethyl] thereby incorporates the pharmacological actions of rasagline, rivastigmine and M30, and is therefore relevant to the comorbidities underlying Alzheimer’s disease (AD), Parkinson’s disease (PD) and Lewy body disease (LBD) (cf., Braak and Braak, 1991). The incidence of depressive symptoms in AD and PD patients is of major importance in attempts to understand comorbid brain pathologies (McDonald et al., 2003; Leentjens, 2004; Shih et al., 2004; Veazey et al., 2005). An antidepressant action of ladostigil was observed using the forced swim test (e.g., Borsini and Meli, 1988) in laboratory rats and mice (Weinstock et al., 2000b). Concurrently, an anti-Parkinsonian action of the compound as a result of its MAO-A and MAO-B inhibiting properties (Finberg et al., 1996; Huang et al., 1999) was indicated (Wu et al., 2000; Gal et al., 2005). The findings presented by Youdim et al. (2001; 2005; 2006; Youdim and Weinstock, 2002; Youdim, 2003; Youdim and Buccafusco, 2005) demonstrate a drug treatment scenario of dual-action in comorbid disorders through an anti-apoptotic-neuroprotective activity and ability to modulate the processing of amyloid protein precursor.

The treatment of comorbid disorders may be difficult. Psychopathy incorporates a myriad of comorbidities (Blair, 2001) and is particularly difficult to treat (cf., Gabbard, 2005). Psychopathy is defined by antisocial behaviour and by emotional impairment (Patrick, 1994), e.g., lack of guilt, and an array of dysfunctional behaviours including impulsivity (Hare, 1991; Blair, 1995, 2003; Hart and Hare, 1996). The neural bases of the disorder encompass dysfunctioning in the amygdala (Blair et al., 1999; Kiehl et al., 2001), ventral frontal areas (LaPierre et al., 1995), prefrontal grey matter (Raine et al., 2000), the medial orbitofrontal cortex (Anderson et al., 1999; Völlm et al., 2004), lateral orbitofrontal cortex (Völlm et al., 2006), the medial PFC (Raine et al., 1994) and the anterior and posterior cingulate cortex (Muller et al., 2003; Völlm et al., 2006). This involvement of multiple brain regions underscores the complexity of psychopathy and the challenges of finding effective treatments.
COMORBID FEATURES OF PSYCHIATRIC AND MOVEMENT DISORDERS

In a new animal model developed by Jay and colleagues, stress was shown to alter synaptic plasticity and impair the limbic-frontal pathways (Dupin et al., 2006). Because mifepristone attenuated this process, it was evident that glucocorticoid receptors mediated the stress-induced response. Also, because the fronto-hippocampus pathway was impaired along with long-term potentiation (LTP) and because the anterior cingulate/orbitofrontal cortices were suppressed, the model replicates comorbid features of schizophrenia and depression. These effects can be prevented or reversed by treatment with the atypical antipsychotic agent clozapine and antidepressants including tianeptine.

Clinical and human counterparts to the model of Dupin et al. (2006) include verbal memory retrieval in schizophrenic patients, reflecting hippocampal and PFC dysfunction (Heckers et al., 1998) and emotional blunting in schizophrenia or depression, reflecting amygdalar dysfunction (Drevets et al., 2002). Brain-derived neurotrophic factor (BDNF), is hypothesized to be the cohesive element in features comorbid in schizophrenia and depression. It is over-expressed in the PFC and basolateral amygdala of the stress-evoked animal model, is thought to be disrupted in both schizophrenia and depression, and is altered by antipsychotic and antidepressant drugs.

The fronto-limbic inhibition addressed above, as well as changes in the visual cortex, can be observed in schizophrenic patients with fMRI and PET imaging using 18-fluoro-deoxy-glucose (FDG) during an attention task (Molina et al., 2005a,b,c,d). The overactive frontal region in schizophrenia and associated reduced inhibitory function in the PFC has been recognized for many years (Stevens et al., 1998; Curtis et al., 1999). Moreover there is a reduction in markers for γ-aminobutyric acid (GABA) including glutamic acid decarboxylase and the GABA transporter (Simpson et al., 1989; Akbarian et al., 1995; Pierri et al., 1999) in the prefrontal area in schizophrenia (Volk et al., 2002).

Increased limbic activity accompanies reduced PFC inhibition, and this can be reversed at least in part with clozapine and olanzapine; both suppress positive (psychosis, disorganization) and negative features (emotional blunting). Simultaneously, recovery of GABA function seems to occur in concert with the symptomatic improvement observed with atypical antidepressants. The changes in activity of selective brain regions in psychiatric disorders and psychotropic drug-induced changes in activity that associate with therapeutic recovery can now be assessed through imaging technology and minimal invasiveness to patients.

In an enveloping and insightful view of three dopaminergic disorders, namely PD, schizophrenia and ADHD, Riederer and colleagues have addressed common features to derive a unique hypothesis regarding dysfunctions in basal ganglia and thalamus that can account for pathophysiologival features of these disorders (Mehler-Wex et al., 2006). For example, in PD, marked by nigrostriatal neuronal degeneration and decreased dopaminergic inputs to the basal ganglia, there is consequent overactivity of basal ganglia output and associated inhibition of the thalamo-cortical drive, resulting in the bradykinesia, akinesia and other cardinal features of parkinsonism. In contrast, in schizophrenia there is apparent overactivity in dopaminergic inputs to the basal ganglia resulting in disinhibition of the thalamo-cortical drive, leading to motor hyperactivity, as well as dysfunctions of attention, perception, affect, and information processing. In ADHD, marked by hyperactivity and inattention, there are features overlapping with schizophrenia, but psychostimulants promote a return to normalcy. Therefore, in ADHD one cannot yet associate under- or over-activity of dopaminergic neurotransmission with the disorder. As an additional complication, there is a greater incidence of psychosis in parkinsonians, although this may be iatrogenic.

In their model Mehler-Wex et al. (2006) highlighted the opposing roles of DA and glutamate neurotransmission. In akinesia, as in untreated PD and in neuroleptic-treated schizophrenia, DA exocytosis in the nigrostriatal tract would be reduced, and glutamate exocytosis in the corticostratiacl tract would be increased. In hyperkinesia, as in L-DOPA-treated PD or in untreated ADHD, DA exocytosis would be enhanced and glutamate exocytosis would be suppressed in the respective tracts or brain regions. In limbic areas, during psychosis, the changes in DA and glutamate transmission would mirror those observed in basal ganglia dur-
ing hyperkinesia.

Tardive dyskinesia, induced by long-term treatment with classical (typical) antipsychotics, is related to "unopposed" block of DA D₂-like receptors, resulting in supersensitivity. Tardive dyskinesia is relatively infrequent with atypical antipsychotics such as clozapine, however, which blocks D₂ and 5-HT₂A receptors and thereby oppose a reflexive enhancement of DA release that normally accompanies D₂ receptor blockade (see Mehler-Wex et al., 2006). In this regard, Kostrzewa et al. (2007) developed a model of tardive dyskinesia using rats in which the nigrostriatal dopaminergic tract was largely destroyed early in postnatal ontogeny by 6-hydroxydopamine (6-OHDA) treatment. When these rats were exposed for one year to haloperidol (1.5 mg/kg/day) in adulthood, a spontaneous increase in vacuous chewing movements (VCMs), analogous to that observed in humans with tardive dyskinesia, developed at 10 weeks vs. 12 weeks in rats without 6-OHDA treatment. Also, the number of VCMs in haloperidol-treated 6-OHDA-lesioned rats was approximately twice that observed in haloperidol-treated non-lesioned rats (Huang and Kostrzewa, 1997). Furthermore, whereas VCM number in chronic haloperidol-treated rats reverts to normal after haloperidol is withdrawn as a treatment even after one year (Waddington, 1990), in the 6-OHDA-lesioned rats that had been exposed to haloperidol for one year there was persistence of the high number of VCMs for at least 8 months (when the study was terminated) after haloperidol had been withdrawn as a treatment (Huang and Kostrzewa, 1994; Huang et al., 1997). This latter event, the first occurrence in rodents for persistence of VCMs during the haloperidol-withdrawal phase, mirrors the dysfunction in humans with tardive dyskinesia. This represented a previously unavailable model to study drugs which might be useful for alleviating tardive dyskinesia after discontinuance of antipsychotic medication.

As shown in Table I of Kostrzewa et al. (2007), the DA D₁ receptor antagonist SCH 23390 failed to attenuate vacuous chewing during the haloperidol-withdrawn period in those rats that had been exposed to haloperidol for one year. Also, the DA D₂-like receptor blockers spiperone and metoclopramide were ineffective in this regard, as were the muscarinic blocker scopolamine, the GABAₐ receptor agonist muscimol, the NMDA receptor blockers ketamine or MK-801, the alpha-adrenoceptor blockers phenolamine and phenoxybenzamine, the opioid mu receptor agonist morphine and mu receptor antagonist naloxone, the adenosine A₂A receptor antagonist theophylline and the histamine H₁ receptor blockers cyproheptadine and ranitidine. These studies eliminated a number of receptors as possible sites for the indicated tardive dyskinesia-like behaviors.

Although the 5-HT₁A receptor blocker pindolol and 5-HT₂A receptor blocker ketanserin were similarly ineffective, the 5-HT₂ receptor antagonists mianserin or mesulergine effectively attenuated VCM number in rats displaying tardive dyskinesia. Similarly, the atypical antipsychotics clozapine and ritanserin were acutely effective in reducing VCMs in rats with tardive dyskinesia. Therefore, although there are element of dopamine receptor supersensitivity (Kostrzewa, 1995) in rats with tardive dyskinesia, it is significant that dopamine D₁- and D₂-like receptor blockers did not eliminate the high number of VCMs in these rats. Of the assorted agents tested, only those with prominent 5-HT₁ receptor-blocking activity were effective in acutely reversing the tardive dyskinesia. Because the 5-HT₁ receptor blockers pindolol and ketanserin were ineffective, and on the basis of this study and others in which 5-HT receptor blockers attenuated VCMs in rats (Gong et al., 1992; 1993), we propose that 5-HT₂C receptors are suitable targets for drugs that might have a potential to effectively treat tardive dyskinesia in humans.

CONCLUSIONS

The defining symptoms of more than one neuropsychiatric disorder may coexist in the same individual. Examples include substance abuse and schizophrenia, OCD and schizophrenia, epilepsy and affective disorders, and schizophrenia and affective disorders. On the other hand, certain symptoms may be common to many disorders. Impulsivity, for example, is often found in drug abuse, OCD, ADHD and bipolar disorder; aggressiveness often co-occurs with impulsivity. Thus, psychiatric diagnoses are often complicated by overlapping symptoms suggestive of more than one disorder.

The PFC was implicated in comorbid schizophre-
nia plus OCD but also in impulsivity. NE and 5-HT, long thought to dysfunction in affective disorders, also were implicated in epilepsy. Eventually biological psychiatry might see the reclassification of psychiatric disorders according to specific symptoms and their known neural substrates.

Novel therapeutic approaches to the treatment of comorbid psychiatric disorders include a combination of pharmacotherapy with family motivational interviewing and cognitive behavioral therapy for substance abuse plus schizophrenia. These comorbid disorders may also be especially responsive to clozapine perhaps implicating one of clozapine's non-DA targets in comorbid substance abuse and schizophrenia. In some cases, medications, e.g., antipsychotics, that effectively reduce some symptoms of a disorder may cause others, raising the possibility of iatrogenic comorbidity. Novel pharmacological agents that combine one or more actions, e.g., l adostigil, offer another therapeutic approach to comorbid disorders. The search for brain substrates of specific symptoms will continue to lead to the development of new therapeutic approaches that eventually will combine maximal treatment effectiveness with minimal iatrogenic consequences.

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