Original Article

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Neurobiology of Comorbid Substance Use Disorders and Psychiatric Disorders

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Current State of Evidence

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Abstract

Background: ''Dual disorder'' or ''dual diagnosis'' refers to the co-occurrence of substance use disorder and psychiatric disorders. Prospective studies have shown that treatment outcomes, such as symptom levels, hospitalization rates, housing stability, and functional status, are worse among the patients with dual disorders as compared with those who have either of these disorders.

Objectives: The current article is aimed at reviewing the current state of evidence on neurobiology of dual disorders. Given the high prevalence of co-occurrence of substance use disorder and psychiatric disorders, it is important to explore the various facets of this association. The current review assimilates the information on neurobiological research on dual disorders and helps the readers gain insights into the current understanding on this theme.

Methods: The electronic database of PubMed was searched for relevant publications.

Results: The studies included in the review belonged to various domains of neurobiology including neuropathology, structural neuroimaging, functional neuroimaging, genetics, neurochemicals/neuroreceptors, and neuroendocrinology. Forty studies were included in the review.

Conclusions: Most of the issues related to the neurobiology of dual disorders remain inadequately studied. However, the current evidence suggests that the individuals with co-occurring disorders are likely to differ from those with either substance use disorders or psychiatric disorders alone on various neurobiological aspects. Hence, it is imperative to systematically study the various neurobiological aspects of dual disorders in the future.

Keywords: comorbidity, dual diagnosis, dual disorders, mental disorders, psychiatric disorder, substance use disorders

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INTRODUCTION

"Dual disorder" or "dual diagnosis" refers to the co-occurrence of substance use disorder and mental disorders (Wittchen, 1996). The relationship between the two is complex. A large proportion of individuals with mental illness also experience substance-use-related problems. Similarly, individuals with disorders related to psychoactive substance use are at an increased risk of experiencing mental illness. Studies have suggested that nearly one third of people with all mental illnesses and approximately half of people with severe mental illnesses (including bipolar disorder and schizophrenia) also experience substance abuse. Conversely, more than one third of all alcohol abusers and more than half of all drug abusers also experience mental illnesses. The rate of co-occurrence of psychiatric disorders and substance use disorders is high even among those seeking treatment (Singh & Balhara, 2016). Despite the high prevalence of co-occurrence of psychiatric disorders and substance use disorders, there is proportionately limited research on dual disorders.

Prospective studies have shown that treatment outcomes, such as symptom levels, hospitalization rates, housing stability, and functional status, are worse among the patients with dual disorders as compared with those who have either of these disorders (Linszen, Dingemans, & Lenior, 1994; Swofford, Kasckow, Scheller-Gilkey, & Inderbitzin, 1996). Hence, it is imperative to study the various facets of dual disorders systematically. The current article is aimed at reviewing the current state of evidence on neurobiology of dual disorders.

METHODOLOGY

Search Strategy

The electronic database of PubMed was searched for relevant publications. The search was carried out in July 2016 and included publications indexed in PubMed July 2016. Boolean

search was carried out using combinations of "neurobiology" and "diagnosis, dual (psychiatry)"; "functional neuroimaging" and "diagnosis, dual (psychiatry)"; "neurotransmitter agents" and "diagnosis, dual (psychiatry)"; "genetics" and "diagnosis, dual (psychiatry)"; "receptors, neurotransmitter" and "diagnosis, dual (psychiatry)"; "brain" and "diagnosis, dual (psychiatry)"; "electrophysiology" and "diagnosis, dual (psychiatry)"; and "neuroendocrinology" and "diagnosis, dual (psychiatry)." In addition, search was carried out using the MeSH term "diagnosis, dual (psychiatry)" alone. An additional published material was identified from the bibliography of the studies screened and evaluated. The study included literature published in peer-reviewed journals. Authors were not contacted for unpublished materials.

Study Selection

For the purpose of the present review, English-language peer-reviewed studies conducted among human subjects were included. Previous reviews were excluded from the present review. In addition, animal studies were also excluded from the present review.

Data Extraction

Information was extracted using a structured proforma from the studies that met the abovementioned inclusion and exclusion criteria. Data were extracted pertaining to the various subdomains of neurobiology, namely, neuropathology, structural neuroimaging, functional neuroimaging, genetics, neurotransmitters and neurotransmitter receptors, electrophysiology, and neuroendocrinology, The information was extracted by two authors using predefined criteria.

RESULTS

Study Selection and Characteristics

The search results and study selection have been presented in Figures 1 and 2.

Fifty-five relevant manuscripts were found after search using the search term "diagnosis, dual (psychiatry)." Forty of these studies were finally included in the current review. Fifteen studies were excluded for reasons specified in Figure 1. Boolean search combining different neurobiology-related terms with "diagnosis, dual (psychiatry)" resulted in 52 relevant studies. Thirty-one of these studies were included in the current review. The others were excluded because of reasons specified in Figure 2. The studies included in the current review have been listed in Table 1.

The studies included in the review belonged to the following domains of neurobiology: neuropathology (Hercher et al., 2009; Miguel-Hidalgo et al., 2002, 2006), structural neuroimaging (De Bellis et al., 2005; Mathalon et al., 2003; Sameti et al., 2011; Scheller-Gilkey et al., 1999; Schiffer et al., 2010; Sullivan et al., 2003; Woodward et al., 2006), functional neuroimaging (Bourque et al., 2013; Cornelius et al., 2010; Joyal et al., 2007; Mancini-Marïe et al., 2006; Potvin et al., 2007; Thompson et al., 2013), genetics (Cheah et al., 2014; Gokturk et al., 2008; Huang et al., 2008; Johann et al., 2003; Lee et al., 2010; Nellissery et al., 2003; Onwuameze et al., 2013; Pierucci-Lagha et al., 2004; Verhagen et al., 2009; Yang et al., 2012, 2014; Zai et al., 2014; Zammit et al., 2007), neurochemicals/neuroreceptors (Araos et al., 2015; Gerra et al., 1994, 1997, 1998; Miller et al., 1986; Pavón et al., 2013; Potvin et al., 2008; Szobot et al., 2008; Thompson et al., 2012), and neuroendocrinology (Gerra et al., 2000; Karlović et al., 2004).

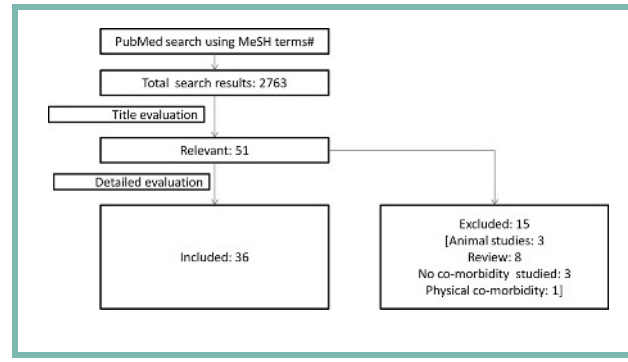

Figure 1. Search algorithm and study selection. [a]Mesh terms used: ''neurobiology'' and ''diagnosis, dual (psychiatry)''; ''functional neuroimaging'' and ''diagnosis, dual (psychiatry)''; ''neurotransmitter agents'' and ''diagnosis, dual (psychiatry)''; ''genetics'' and ''diagnosis, dual (psychiatry)''; ''receptors, neurotransmitter'' and ''diagnosis, dual (psychiatry)''; ''brain'' and ''diagnosis, dual psychiatry)''; ''electrophysiology'' and ''diagnosis, dual (psychiatry)''; ''neuroendocrinology'' and ''diagnosis, dual (psychiatry)''; and ''diagnosis, dual (psychiatry).''

Table 2 summarizes the salient features and findings of these studies.

DISCUSSION

The salient features of these studies on neurobiology of dual disorders included in the current review have been discussed below.

Substances Studied

Alcohol. All the published studies on neuropathology (Hercher et al., 2009; Miguel-Hidalgo et al., 2002, 2006) and structural neuroimaging (De Bellis et al., 2005; Mathalon et al., 2003; Sameti et al., 2011; Sullivan et al., 2003; Woodward et al., 2006) of comorbid disorders have been conducted among subjects with alcohol use disorders. Most of the studies on genetics have been conducted among subjects with alcohol use disorders (Cheah et al., 2014; Gokturk et al., 2008; Huang et al., 2008; Johann et al., 2003; Lee et al., 2010; Nellissery et al., 2003; Pierucci-Lagha et al., 2004; Verhagen et al., 2009; Zai et al., 2014).

Two studies that assessed the biomarkers/biochemical/neuroreceptors among individuals with disorders have been conducted among subjects with alcohol use disorders (Miller et al., 1986; Thompson et al., 2012). One study on neuroendocrinological aspects of dual disorders included subjects with alcohol use disorders (Karlović et al., 2004).

Opioids. One of the studies on genetics has been conducted among subjects with opioid use disorders (Yang et al., 2012). Three of the studies that assessed the biomarkers/biochemical/neuroreceptors among individuals with disorders have been conducted among

MeSH Search Term	Total Results	Relevant Studies	Excluded	Included
Diagnosis, Dual (Psychiatry)	2763	51	Animal studies: 3 Review: 8 No co-morbidity studied: 3 Physical co-morbidity: 1	36
Neurobiology AND Diagnosis, Dual (Psychiatry)	1	1	0	1
Functional Neuroimaging AND Diagnosis, Dual (Psychiatry)	7	6	Animal studies: 2	4
Neurotransmitter Agents AND Diagnosis, Dual (Psychiatry)	42	6	Review: 2	4
Genetics AND Diagnosis, Dual (Psychiatry)	112	2	Review: 1 No co-morbidity studied:1	0
Receptors, Neurotransmitter AND Diagnosis, Dual (Psychiatry)	13	6	Review: 3	3
Brain AND Diagnosis, Dual (Psychiatry)	51	27	Animal studies: 4 Review: 5 No co-morbidity: 3	15
Electrophysiology AND Diagnosis, Dual (Psychiatry)	0	0	0	0
Neuroendocrinology AND Diagnosis, Dual (Psychiatry)	0	0	0	0

Figure 2. Search results using various search terms.

subjects with opioid use disorders (Gerra et al., 1994, 1997, 1998). One study on neuroendocrinological aspects of dual disorders (Gerra et al., 2000) and one study on genetics (Yang et al., 2014) included subjects with opioid use disorders.

Cannabis. One of the studies on genetics has been conducted among subjects with cannabis use disorders (Onwuameze et al., 2013). Two functional neuroimaging studies (Bourque et al., 2013; Cornelius et al., 2010) focused on cannabis use disorders.

Cocaine. Two studies assessed the biomarkers/biochemical/neuroreceptors among individuals with cocaine use disorders (Araos et al., 2015; Pavón et al., 2013).

Multiple Substances

One of the studies on genetics has been conducted among subjects with tobacco and/or cannabis use disorders (Zammit et al., 2007). Two structural neuroimaging studies included subjects with two or more different substance use disorders (Scheller-Gilkey et al., 1999; Schiffer et al., 2010). Except for the two functional neuroimaging studies (Bourque et al., 2013; Cornelius et al., 2010) that focused on cannabis use disorders, the rest included subjects with two or more different substance use disorders (Joyal et al., 2007; Mancini-Marïe et al., 2006; Potvin et al., 2007; Thompson et al., 2013). Two studies that assessed the biomarkers/biochemical/neuroreceptors among individuals with disorders have been conducted among subjects with more than one substance use disorders (Potvin et al., 2008; Szobot et al., 2008).

Psychiatric Disorders Studied

Two of the three studies on neuropathology of dual disorders were conducted among subjects with suicidal behavior (Hercher et al., 2009; Miguel-Hidalgo et al., 2006). The third study was conducted among subjects with depressive disorder (Miguel-Hidalgo et al., 2002). Most of the studies on structural neuropathology of dual disorders have been conducted among subjects with schizophrenia (Mathalon et al., 2003; Scheller-Gilkey et al., 1999; Schiffer et al., 2010; Sullivan et al., 2003). Two studies included subjects with multiple psychiatric disorders (De Bellis et al., 2005; Sameti et al., 2011), and one was conducted among subjects with posttraumatic stress disorder (PTSD; Woodward et al., 2006). Except one study that assessed subjects exposed to a threat paradigm (Cornelius et al., 2010), the rest of the studies on functional neuroimaging of dual disorders were conducted among subjects with schizophrenia (Bourque et al., 2013; Joyal et al., 2007; Mancini-Marïe et al., 2006; Potvin et al., 2007; Thompson et al., 2013). Studies exploring genetics of dual disorders have included subjects with attention deficit hyperactivity disorder (ADHD; Johann et al., 2003); antisocial personality disorder (ASPD; Yang et al., 2012); borderline personality disorder (BPD; Yang et al., 2014); depressive disorder (Nellissery et al., 2003; Pierucci-Lagha et al., 2004); depressive disorder and anxiety disorder (Lee et al., 2010); depressive disorder, dysthymia, and generalized anxiety disorder (Verhagen et al., 2009); multiple psychiatric disorders (Gokturk et al., 2008; Huang et al.,

TABLE 1 Studies That Have Explored Neurobiology of Comorbid Substance Use Disorder and Common Mental Disorders

Publication	Type of Publication	Study Population	Psychoactive Substance Studied	Mental Disorder Studied
Neuropathology				
Miguel-Hidalgo et al., 2002	Case-control study, postmortem biopsy	Adults	Alcohol	Depression
Miguel-Hidalgo, Overholser, Meltzer, Stockmeier, & Rajkowska, 2006	Case-control study, postmortem biopsy	Adults	Alcohol	Suicide
Hercher et al., 2009	Case-control study, postmortem biopsy	Adults	Alcohol	Suicide
Structural neuroimaging				
Scheller-Gilkey, Lewine, Caudle, & Brown, 1999	Observational, MRI	Adults	Multiple	Schizophrenia
Mathalon, Pfefferbaum, Lim, Rosenbloom, & Sullivan, 2003	Chart review, MRI	Adults	Alcohol	Schizophrenia
Sullivan, Rosenbloom, Serventi, Deshmukh, & Pfefferbaum, 2003	Case-control study, MRI	Adults	Alcohol	Schizophrenia
De Bellis et al., 2005	Case-control study, MRI	Adolescents, young adults	Alcohol	Multiple
Woodward et al., 2006	Observational study, MRI	Adults	Alcohol	PTSD
Schiffer et al., 2010	Case-control study, MRI	Adults	Multiple	Schizophrenia
Sameti, Smith, Patenaude, & Fein, 2011	Case-control study, MRI	Adults	Alcohol	Multiple
Functional neuroimaging				
Mancini-Marïe et al., 2006	Experimental study, fMRI	Adults	Multiple	Schizophrenia
Joyal et al., 2007	Experimental study, fMRI	Adults	Multiple	Schizophrenia
Potvin, Mancini-Marie, Fahim, Mensour, & Stip, 2007	Experimental, fMRI	Adults	Alcohol and/or cannabis	Schizophrenia
Cornelius, Aizenstein, & Hariri, 2010	Experimental, BOLD fMRI	Adults	Cannabis	Threat paradigm
Bourque et al., 2013	Experimental, fMRI	Adults	Cannabis	Schizophrenia
Thompson et al., 2013	Interventional, [^{11}C]raclopride positron emission tomography	Adults	Multiple	Schizophrenia
Genetic				
Johann, Bobbe, Putzhammer, & Wodarz, 2003	Observational study	Adults	Alcohol	ADHD
Nellissery et al., 2003	Observational study	Adults	Alcohol	Depressive disorder
Pierucci-Lagha et al., 2004	Intervention, double blind, placebo controlled	Adults	Alcohol	Depressive disorder
Huang, Lu, Ma, Shy, & Lin, 2008	Observational study	Adults	Alcohol	Multiple
Zammit et al., 2007	Case-control study	Adults	Tobacco, cannabis	Schizophrenia
Gokturk et al., 2008	Case-control study	Adolescents and adults	Alcohol	Multiple
Verhagen et al., 2009	Observational study	Adults	Alcohol	Depression, dysthymia, GAD

(continues)

TABLE 1 Studies That Have Explored Neurobiology of Comorbid Substance Use Disorder and Common Mental Disorders, Continued

Publication	Type of Publication	Study Population	Psychoactive Substance Studied	Mental Disorder Studied
Lee et al., 2010	Observational study	Adults	Alcohol	Depression, anxiety
Yang, Kavi, Wang, Wu, & Hao, 2012	Case-control study	Adults	Opioid	ASPD
Onwuameze et al., 2013	Observational	Adults	Cannabis	Schizophrenia
Cheah et al., 2014	Case-control study	Adults	Alcohol	Schizophrenia
Yang et al., 2014	Case-control study	Adults (female)	Opioid	Borderline personality disorder
Zai et al., 2014	Observational study	Adults	Alcohol	Schizophrenia
Biomarkers/biochemical/neuroreceptors				
Miller, Barasch, Sacks, Levitan, & Ashcroft, 1986	Observational	Adults	Alcohol	Depression
Gerra et al., 1994	Interventional	Adults	Opioids	Personality disorder and aggression
Gerra et al., 1997	Interventional	Adults	Opioid	Depressive disorder
Gerra et al., 1998	Interventional	Adults	Opioids	Anxiety disorders (anxious cluster)
Potvin et al., 2008	Interventional	Adults	Multiple	Schizophrenia
Szobot et al., 2008	Interventional, SPECT	Adolescents	Multiple	ADHD
Thompson, Cruz, Olukotun, & Delgado, 2012	Case-control study, postmortem biopsy	Adults	Alcohol	Suicide
Pavón et al., 2013	Case-control study	Adults	Cocaine	Multiple
Araos et al., 2015	Case-control study	Adults	Cocaine	Multiple
Neuroendocrine study				
Gerra et al., 2000	Intervention	Adults	Opioid	Depression
Karlović, Marusić, & Martinac, 2004	Case-control study	Adults	Alcohol	PTSD

ADHD = attention deficit hyperactivity disorder; ASPD = antisocial personality disorder; BOLD = blood oxygen level dependent; fMRI = functional magnetic resonance imaging; GAD = generalized anxiety disorder; PTSD = posttraumatic stress disorder; SPECT = single-photon emission computed tomography.

2008); and schizophrenia (Cheah et al., 2014; Onwuameze et al., 2013; Zai et al., 2014). Studies exploring neurochemical aspects of comorbid disorders have been conducted among subjects with ADHD (Szobot et al., 2008), anxiety disorders (Gerra et al., 1998), depressive disorders (Gerra et al., 1997; Miller et al., 1986), schizophrenia (Potvin et al., 2008), siblings with personality disorders (Gerra et al., 1994), suicidal behavior (Thompson et al., 2012), and multiple psychiatric disorders (Araos et al., 2015; Pavón et al., 2013). Studies exploring neuroendocrinological aspects have been conducted among subjects with depressive disorder (Gerra et al., 2000) and PTSD (Karlović et al., 2004).

Types of Studies

Whereas most of the studies on neurobiology of dual disorders were observational (Araos et al., 2015; Bourque et al., 2013; Cheah et al., 2014; Cornelius et al., 2010; De Bellis et al., 2005; Gokturk et al., 2008; Hercher et al., 2009; Huang et al., 2008; Johann et al., 2003; Joyal et al., 2007; Karlović et al., 2004; Lee et al., 2010; Mancini-Marïe et al., 2006; Mathalon et al., 2003; Miguel-Hidalgo et al., 2002, 2006; Miller et al., 1986; Nellissery et al., 2003; Onwuameze et al., 2013; Pavón et al., 2013; Potvin et al., 2007; Sameti et al., 2011; Scheller-Gilkey et al., 1999; Schiffer et al., 2010; Sullivan et al., 2003; Swofford et al., 1996; Szobot et al., 2008; Thompson et al., 2012; Verhagen et al., 2009; Woodward et al., 2006; Yang et al., 2012, 2014; Zai et al., 2014; Zammit et al., 2007), a few were experimental (Gerra et al., 1994, 1997, 1998, 2000; Pierucci-Lagha et al., 2004; Potvin et al., 2008; Thompson et al., 2013). Most of the observational studies used a case-control design. One double-blind placebo-controlled trial assessed the effect of rapid tryptophan depletion on mood and urge to drink

TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Neuropathology				
Miguel-Hidalgo et al. (2002)	Alcohol dependence with/without depressive symptoms	Postmortem histopathology	Alcohol dependent ($n = 8$ with comorbid depressive symptoms, $n = 9$ without comorbid depressive symptoms), controls ($n = 21$)	Smaller glial cell nuclei and glial density in DLPFC among those with comorbid depressive symptoms
Miguel-Hidalgo et al. (2006)	Alcohol dependence with completed suicide versus nonsuicidal death	Postmortem histopathology	Alcohol dependent ($n = 8$ with completed suicide, $n = 7$ with death due to other causes), controls ($n = 8$)	No difference in the density of neurons and glial cells in the OFC
Hercher et al. (2009)	Alcohol-/non-alcohol-dependent depressed, suicide completers	Postmortem histopathology	Individuals with depression completing suicide ($n = 13$), matched controls having sudden death ($n = 13$)	Increase in glial cell densities in the ACC of alcohol-dependent depressed, suicide completers
Structural neuroimaging				
Scheller-Gilkey et al. (1999)	Schizophrenia with/without comorbid alcohol and drug use	MRI	Individuals with schizophrenia and comorbid alcohol and drug use and with schizophrenia alone ($n = 176$)	No difference between the two groups on brain MRI
Mathalon et al. (2003)	Schizophrenia/schizoaffective disorder with/without alcohol abuse/dependence	MRI	Individuals with schizophrenia or schizoaffective disorder and lifetime alcohol abuse or dependence ($n = 35$), schizophrenia or schizoaffective disorder ($n = 64$), or alcoholism ($n = 62$); controls ($n = 62$)	Higher gray matter volume deficits in dual-disorder group, most prominent in the prefrontal and anterior superior temporal regions of the brain
Sullivan et al. (2003)	Schizophrenia and alcohol dependence	MRI	Individuals with schizophrenia ($n = 27$), individuals with schizophrenia and comorbid alcohol dependence ($n = 19$), individuals with alcohol dependence without comorbid Axis I disorders ($n = 25$), controls ($n = 51$)	Volume deficits in pons in those with dual disorders
De Bellis et al. (2005)	Adolescent-onset alcohol use disorders and mental disorders	MRI	Adolescents and young adults with comorbid adolescent-onset alcohol use disorders and mental disorders (eight men, six women), matched controls (16 men, 12 women)	Dual disorders had smaller prefrontal cortex and prefrontal cortex white matter volumes
Woodward et al. (2006)	Posttraumatic stress disorder (PTSD) and alcohol abuse/dependence	MRI	Combat veterans diagnosed with PTSD and lifetime alcohol abuse/dependence, PTSD without lifetime alcohol abuse/dependence, lifetime alcohol abuse/dependence without PTSD, and PTSD alone ($n = 99$)	Smaller unadjusted hippocampal volume in PTSD than in those without it among those with alcohol abuse/dependence

(continues)

TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders, Continued

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Schiffer et al. (2010)	Schizophrenia and substance use disorder	MRI	Individuals with comorbid schizophrenia and substance use disorder ($n = 12$), those with schizophrenia alone ($n = 12$), matched individuals without schizophrenia ($n = 14$), matched individuals with substance use disorder alone ($n = 13$)	Total gray matter volume deficits largest in individuals with dual disorders
Sameti et al. (2011)	Lifetime history of alcohol use with current or lifetime history of psychiatric disorder	MRI	Long-term abstainers from alcohol (28 men, 24 women), nonalcoholic controls (25 men, 23 women)	Subcortical structures were smaller in volume in those with comorbidity
Functional neuroimaging				
Mancini-Marïe et al. (2006)	Schizophrenia and substance use disorder	fMRI	Patients with schizophrenia and substance use disorder ($n = 12$), those with schizophrenia without substance use disorder ($n = 11$)	Increased activity in the right medial prefrontal cortex, left medial prefrontal cortex, right orbitofrontal cortex, and left amygdala while viewing emotionally negative pictures among those with dual disorders
Joyal et al. (2007)	Schizophrenia with antisocial personality disorder and substance use disorder	fMRI		Higher activation in motor, premotor, and anterior cingulate regions and lower activations in frontal basal cortices in those with schizophrenia, antisocial personality disorder, and substance use disorder during the go/no-go task
Potvin et al. (2007)	Schizophrenia and alcohol and/or cannabis use disorder	fMRI	Individuals with schizophrenia and alcohol and/or cannabis use disorder ($n = 12$), individuals with schizophrenia alone ($n = 11$)	Increased activation in the right superior parietal cortex and the left medial prefrontal cortex in those with dual disorders
Cornelius et al. (2010)	Major depression and comorbid cannabis dependence	fMRI	($n = 6$)	Higher cannabis use associated with lower amygdala reactivity. A decrease in cannabis use was associated with an increase in the amygdala reactivity.
Bourque et al. (2013)	Schizophrenia and cannabis abuse	fMRI	Subjects with comorbid schizophrenia and cannabis abuse ($n = 14$), non-cannabis-abusing subjects with schizophrenia ($n = 14$), controls ($n = 21$)	No significant differences seen between the groups
Thompson et al. (2013)	Schizophrenia and substance dependence	[^{11}C]raclopride positron emission tomography	Unmedicated, drug-free patients with both schizophrenia and substance dependence ($n = 11$), controls ($n = 15$)	Individuals with dual disorders showed blunting of striatal dopamine release

(continues)

TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders, Continued

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Genetics				
Johann et al. (2003)	Alcohol use disorder and ADHD and antisocial personality disorder	Genetic association study	Alcoholics (n = 314, of which 67 had ADHD and 30 had both ADHD and antisocial personality disorder), controls	No differences in 5-HTT genotype or 5-HT2c allele distribution among various groups
Nellissery et al. (2003)	Major depression and alcohol dependence	Genetic association study	Participants with comorbid alcohol dependence and major depression (n = 296 European Americans and n = 16 African Americans), controls (n = 260 European Americans, n = 43 African Americans)	Frequency of the short allele at the SLC6A4 locus of serotonin transporter-linked polymorphic region among various groups
Pierucci-Lagha et al. (2004)	Major depression and alcohol dependence	Genetic association study	Individuals with alcohol dependence and major depressive disorder (n = 14)	Individuals homozygous for long allele of serotonin transporter had greater depression than those with one or two copies of the S allele.
Huang et al. (2008)	Alcohol dependence	Genetic association study	Han Chinese alcohol-dependent individuals (n = 408), controls (n = 282)	No significant differences in the genotype and allele frequencies of hSLC6A2 polymorphisms found between homogeneous subgroups with alcohol dependence and controls
Zammit et al. (2007)	Schizophrenia, cannabis and tobacco use	Genetic association study	Participants with schizophrenia (n = 750), controls (n = 688)	No association was found between schizophrenia and CNR1 or CHRNA7 genotypes, between tobacco use and CHRNA7, and between cannabis use and CNR1 or COMT genotypes
Gokturk et al. (2008)	Females with alcohol addiction	Genetic association study	Women with severe alcohol addiction (n = 110)	Higher frequency of LL 5-HTT genotype (high activity) found in those without comorbid psychiatric disorder. MAOA-VNTR polymorphism did not differ between those with addictions and controls.
Verhagen et al. (2009)	Familial major depression with comorbid psychiatric or substance use disorder	Genetic association study	Individuals with familial major depressive disorder and a comorbid disorder vis-à-vis those with major depressive disorder without that particular comorbidity (n = 233)	An association between the 5-HTTLPR and comorbid alcohol use disorder was observed in women, with S-carriers reporting less alcohol use disorder

(continues)

TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders, Continued

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Lee et al. (2010)	Alcohol dependence with past or current anxiety/depression	Genetic association study	Han Chinese men with anxiety-depressive alcohol dependence (n = 143), controls (n = 240)	ALDH2 polymorphism was associated with comorbid alcohol dependence and a past or current history of anxiety, depressive disorder, or both. A significant association was observed for interaction between ALDH2 and MAOA variants with comorbid alcohol dependence and a history of anxiety, depressive disorder, or both.
Yang et al. (2012)	Men with heroin dependence and antisocial personality disorder	Genetic association study	Male heroin-dependent subjects with antisocial personality disorder (n = 311), male heroin-dependent subjects without antisocial personality disorder (n = 277), controls (n = 194)	Those with 10R allele were at a higher risk of comorbid antisocial personality disorder and heroin dependence. In heroin-dependent patients, individuals carrying 5-HTTVNTR 10R allele and/or DATVNTR 9R allele were at a higher risk of having comorbid antisocial personality disorder, whereas individuals with 5-HTTVNTR 12R/12R and DATVNTR 10R/10R genotypes together were at a lower risk of having antisocial personality disorder.
Onwuameze et al. (2013)	Schizophrenia and cannabis abuse/ dependence	Genetic association study	Individuals with schizophrenia with comorbid marijuana abuse or dependence (n = 235 with schizophrenia)	Individuals homozygous for rs12199654-A and had comorbid schizophrenia with cannabis abuse/ dependence had smaller total cerebral and lobar white matter volumes. Both the genetic variants of the MAPK14 CNR1 diplotypes had additive contribution to white matter volume deficits in individuals with comorbidity.

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TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders, Continued

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Cheah et al. (2014)	Schizophrenia and alcohol dependence	Genotyping BDNF SNPs rs6265 and rs7103411	Schizophrenia group (n = 157, of which 42 were having alcohol use disorder), schizophrenia replication group (n = 235, of which 72 were having comorbid alcohol dependence), alcohol-dependent group with no schizophrenia (n = 231), healthy controls (n = 225)	Allelic association between rs7103411 and comorbid alcohol dependence was found in a sample with primary schizophrenia (p = .044). Allelic association between both BDNF SNPs and comorbid alcohol dependence was found in the replication group (rs6265, p = .006; rs7103411, p = .014). Haplotype analysis showed that the rs6265–rs7103411 A/C haplotype is associated with comorbid alcohol dependence (p = .002).
Yang et al. (2014)	Borderline personality disorder (BPD) and opioid dependence	Genetic association study; studied the polymorphic distributions of 5-HTR2A1438A/G, COMT Val158Met, MAOALPR, DATVNTR, and 5-HTTVNTR	296 female heroin-dependent patients (61 patients with BPD), 101 normal women	Female heroin-dependent subjects with BPD: lower frequency of the high-activity allele (L: 4 repeats [4R]) of MAOALPR when compared with those without BPD (p < .05); higher 5-HTTVNTR 10R/10R genotype frequency than normal female controls (p < .05)
Zai et al. (2014)	Schizophrenia with suicidal behavior with a history of alcohol abuse or dependence	8 single-nucleotide polymorphisms spanning the GABRG2 gene	Schizophrenia with a history of suicidal behavior with a history of alcohol abuse or dependence (n = 197)	Haplotypes of the rs183294 and rs209356 markers were significantly associated with a history of suicide attempt (p < .01) as well as suicide specifier scores (p < .05).
Biomarkers/biochemicals/neuroreceptors				
Miller et al. (1986)	Alcohol dependence and depressive symptoms	Serum prolactin levels	Individuals with alcohol dependence (n = 15)	Increase in serum prolactin levels correlated with Hamilton Depression Rating Scale scores.
Gerra et al. (1994)	Siblings of patients with heroin dependence with comorbid personality disorder	Noradrenergic receptor sensitivity assessment by measuring the growth hormone and beta-endorphin responses after the clonidine stimulation test	Healthy male siblings of those with heroin addiction (n = 16), matched controls (n = 8)	Growth hormone and beta-endorphin responses to clonidine blunted in siblings of those with dual disorders

(continues)

TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders, Continued

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Gerra et al. (1997)	Patients with heroin dependence and their mothers with comorbid major depressive disorder	Serotonergic function assessment using D-fenfluramine stimulation of prolactin and cortisol secretion	Participants with major depressive disorder (n = 20), those without psychopathological features (n = 16), matched controls (n = 10)	Direct correlation between prolactin areas under curve for both mothers and sons in response to the serotonergic agonist, D-fenfluramine. Blunted prolactin and cortisol responses to the D-fenfluramine stimulation among mothers of those with dual disorders. The sons of depressed mothers showed reduced prolactin and cortisol responses to fenfluramine.
Gerra et al. (1998)	Heroin abuse/ dependence and anxiety disorder	Growth hormone response assessment to baclofen challenge	Patients with heroin dependence and abuse (n = 10 with comorbid anxiety disorder, n = 10 without comorbid psychiatric disorder), controls (n = 10)	Growth hormone response to baclofen stimulation blunted among patients with dual disorders
Potvin et al. (2008)	Schizophrenia and alcohol/cannabis use disorder	Peripheral endogenous cannabinoid (anandamide) level measurement	Those with comorbid schizophrenia and alcohol/cannabis use disorders (n = 29), controls (n = 17)	Baseline anandamide levels higher in patients with dual disorders
Szobot et al. (2008)	Adolescents with ADHD with comorbid cannabis and cocaine use disorder	Assessment of the effect of an extended release formulation of methylphenidate on dopamine transporter availability using single-photon emission computed tomography (SPECT) scans with (Tc-99m) TRODAT-1	Adolescents with ADHD with comorbid cannabis and cocaine use disorder (n = 17)	52% reduction of the dopamine transporter binding potential at bilateral caudate and putamen along with a significant reduction in ADHD clinical feature severity with extended-release methylphenidate stimulation
Thompson et al. (2012)	Alcohol dependence and completed suicide	Serotonin receptor (5-HT) and serotonin reuptake transporter (SERT) mRNA measurement	Individuals with alcohol dependence and suicidal behavior (n = 5), alcohol-dependent individuals without suicidal behavior (n = 9), controls (n = 5)	In those with alcohol dependence with suicidal behavior, anxiety symptoms were associated with decreased Brodmann area 24 SERT mRNA levels, and depressive symptoms were associated with Brodmann area 9 5-HT1A mRNA expression

(continues)

TABLE 2 Summary of Findings From Studies Exploring Neurobiology of Dual Disorders, Continued

Name of the Study	Disorders Studied	Technique Used	Participants	Major Findings
Pavón et al. (2013)	Cocaine use disorder with comorbid anxiety and mood disorder	Assessment of free N-acylethanolamines and 2-acyl-glycerols levels	Subjects with cocaine use disorder (n = 88), matched controls (n = 46)	The monounsaturated N-acylethanolamines elevated in patients were dual disorders
Araos et al. (2015)	Cocaine users with comorbid psychiatric disorder	Assessment of tumor necrosis factor alpha chemokine (CC motif) ligand 2/monocyte chemotactic protein 1 and chemokine (CXC motif) ligand 12 (CXCL12)/stromal cell-derived factor 1 (SDF1), interleukin 1 beta (IL1β), chemokine (CX3C motif) ligand 1 (CX3CL1)/fractalkine CXCL12/SDF1	Abstinent cocaine users with comorbid psychiatric disorder (n = 82), age-/sex-/body-mass-matched controls (n = 65)	By cytokines, cocaine users could be categorized into subgroups with increased prevalence of comorbid psychiatric disorders (mood [54%], anxiety [32%], psychotic [30%], and personality [60%] disorders]. IL1β was increased in users with psychiatric disorders relative to those users with no diagnosis.
Neuroendocrinology				
Gerra et al. (2000)	Heroin dependence with comorbid depressive disorder	Central norepinephrine activity measured by growth hormone response to acute stimulation with clonidine, central serotonin activity measured by prolactin and cortisol responses to acute stimulation with D-fenfluramine, central dopaminergic activity measured by the growth hormone and prolactin response to acute administration of bromocriptine	Heroin-dependent patients (n = 14 with comorbid depressive disorder, n = 14 without comorbid psychiatric disorders), controls (n = 22)	Higher growth hormone response to bromocriptine observed in those with dual disorders
Karlović et al. (2004)	PTSD and alcohol dependence	Measurement of serum levels of free triiodothyronine, total triiodothyronine, free thyroxine, total thyroxine, and thyroid-stimulating hormone	Soldiers with combat-related chronic PTSD (n = 43), those with PTSD comorbid with alcohol dependence (n = 41), controls (n = 39)	Patients with chronic combat-related PTSD had higher free triiodothyronine levels.

ACC = anterior cingulate cortex; ADHD = attention deficit hyperactivity disorder; BDNF SNPs = brain derived neurotrophic factor gene single nucleotide polymorphisms; DLPFC = dorso-lateral prefrontal cortex; fMRI = functional magnetic resonance imaging; OFC = orbito-frontal cortex.

among patients with alcohol dependence and major depressive disorder (Pierucci-Lagha et al., 2004). The other interventional studies assessed neuroendocrinological responses to biochemical challenges among subjects with opioid dependence with comorbid anxiety disorder (Gerra et al., 1998), depressive disorder (Gerra et al., 1997), and depressive disorder and personality disorder (Gerra et al., 1994) and functional neuroimaging among subjects with comorbid substance use disorder and schizophrenia (Thompson et al., 2013).

Gender and Age Groups Studied

Most of the studies have been conducted among adult men with the exception of 15 studies that have also included female subjects (Cornelius et al., 2010; Gerra et al., 1997; Gokturk

et al., 2008; Mancini-Marïe et al., 2006; Miguel-Hidalgo et al., 2002, 2006; Onwuameze et al., 2013; Pavón et al., 2013; Pierucci-Lagha et al., 2004; Potvin et al., 2007, 2008; Sameti et al., 2011; Scheller-Gilkey et al., 1999; Thompson et al., 2013; Verhagen et al., 2009) and adolescents (De Bellis et al., 2005; Gokturk et al., 2008; Szobot et al., 2008). Three studies exclusively included female subjects (Gerra et al., 1997; Gokturk et al., 2008; Yang et al., 2014). In addition, some studies have included relatives of the individuals with dual disorders or substance use disorders (Gerra et al., 1994, 1997).

Existing Evidence on Neurobiology of Dual Disorders

The existing literature on neurobiology of dual disorders has explored only a few aspects related to this association.

Studies on neuropathology. Postmortem neuropathology studies suggest that, among individuals with alcohol dependence who die of suicide, the structural pathology in the cerebral cortex is related mainly to alcohol use status (Hercher et al., 2009; Miguel-Hidalgo et al., 2002, 2006). Whereas comorbid depressive disorder exacerbates some of this pathology, completed suicide is not associated with any additional changes in brain morphology in these regions.

Studies on structural neuroimaging. All the structural imaging studies have used magnetic resonance imaging (MRI) as a tool of investigation. Comorbidity of alcohol use disorder and schizophrenia worsens the adverse effect of either of the two conditions on certain regions of the brain (overall gray volume of the cerebral cortex, prefrontal gray matter volume; Mathalon et al., 2003) and regions not affected directly by schizophrenia (pontine structures; Sullivan et al., 2003). Among individuals with comorbid alcohol dependence and psychiatric disorders, a smaller prefrontal cortex is associated with early-onset drinking (De Bellis et al., 2005). In addition, it is likely that comorbid psychiatric disorder among those with alcohol dependence interferes with the recovery in brain volume deficit in subcortical regions observed after long-term abstinence from alcohol among individuals with alcohol dependence alone. Individuals with comorbid alcohol dependence and PTSD have a relatively smaller hippocampus volume, which could explain the increased risk of PTSD among those with alcohol dependence (Woodward et al., 2006). Comorbidity of schizophrenia and substance use disorders worsens the adverse effects associated with substance use in certain regions of the brain not affected directly by schizophrenia (anterior cingulate, frontopolar and superior parietal regions). The additive deficits associated with comorbid substance use disorder and schizophrenia are noticeable in nonplanning impulsivity as opposed to functional executive deficits that remain largely unaffected by the comorbidity (Schiffer et al., 2010).

The studies have implicated diverse regions of the brain among those with dual disorders. Overall gray matter volume of the cerebral cortex, prefrontal gray matter volume, pontine structures, and hippocampus are some of the brain regions that have been the focus of interest in these studies. More importantly, most of the findings from individual studies remain unreplicated. Hence, it is difficult to draw conclusive inferences based on the existing evidence.

Studies on functional neuroimaging. Most of the functional neuroimaging studies have employed functional MRI as a tool of investigation. Other functional neuroimaging tools used in these studies are blood-oxygen-level-dependent functional MRI and [^{11}C]raclopride positron emission tomography. Among individuals with comorbid cannabis use disorder and schizophrenia, emotional memory and prefrontal lobe functioning are relatively better preserved as compared with those with schizophrenia alone (Bourque et al., 2013). Among individuals with comorbid schizophrenia and substance (heterogeneous) use disorders, the functioning of the medial prefrontal cortex and socioemotional processing are relatively better preserved (Thompson et al., 2013). In addition, there is a transient amphetamine-induced positive symptom change accompanied by a blunted dopamine release in these individuals. The frontal basal cortices are significantly less activated in individuals with comorbidity (schizophrenia, substance use disorders, and ASPD) during the assessment of measures of impulse control as compared with individuals with schizophrenia only and healthy controls (Joyal et al., 2007). However, higher activations are observed in frontal motor, premotor, and anterior cingulate regions in individuals with comorbidity. The findings suggested that emotional memory and prefrontal lobe functioning are relatively better preserved in individuals with comorbid schizophrenia and cannabis abuse relative to non-cannabis-abusing individuals with schizophrenia. A decrease in cannabis use among individuals with comorbid cannabis dependence and depressive disorder after fluoxetine administration is associated with an increase in amygdala reactivity among individuals who show a decrease in cannabis use after the treatment trial (Cornelius et al., 2010). Although the recognition of positive and negative emotions is impaired in non-cannabis-abusing subjects with schizophrenia relative to healthy controls, there is little difference between those with comorbid schizophrenia and cannabis abuse and healthy controls. Moreover, different regions of the brain get activated in response to such stimuli among individuals with comorbidity as compared with those with schizophrenia alone. Striatal dopamine release in response to amphetamine challenge is impaired among subjects with comorbid schizophrenia and substance dependence (Thompson et al., 2013).

Studies on genetics. Among the individuals with comorbid alcohol use disorder and depressive disorder, the frequency of the short allele at the SLC6A4 locus of serotonin (5-HT) transporter-linked polymorphic region is similar to those with depressive disorder alone (Nellissery et al., 2003). In addition, serotonergic neurotransmission has been found to have a role in modulating mood and alcohol urges among these individuals. The effect of the 5-HT transporter-linked polymorphic region polymorphism on major depressive disorder among those with alcohol use disorders is codependent on the presence of comorbid disorders and gender.

Different variants of monoamine oxidase A (MAOA)-uVNTR polymorphisms modify the protective effects of the ALDH2*2 allele on individuals with comorbid alcohol use disorder and anxiety and depressive disorders in Han Chinese (Gokturk et al., 2008). Among women with comorbid alcohol use disorder and psychiatric disorder, there is a significantly higher frequency of the LL 5-HTT genotype. Moreover, contrary to findings among men, among women with alcohol use disorder, aggressive antisocial behavior is significantly linked to the presence of the high-activity MAOA allele. Among individuals with comorbid alcohol use disorder and ADHD, functional, relevant serotonin transporter gene promoter and the 5-HT2c receptor Cys23Ser polymorphism do not seem to contribute to the common genetic predisposition of alcohol dependence and ADHD (Johann et al., 2003). Among heroin-dependent patients, individuals carrying 5-HTTVNTR 10R allele or/and DATVNTR 9R allele are at higher risks of comorbid ASPD (Yang et al., 2012). On the other hand, individuals with 5-HTTVNTR 12R/12R and DATVNTR 10R/10R genotypes together are at lower risks of ASPD. Individuals with comorbid schizophrenia and cannabis abuse/dependence who are homozygous for rs12199654-A have smaller total cerebral and lobar white matter volumes. A comparative observational study revealed an allelic association between rs7103411 and comorbid alcohol dependence in a sample with primary schizophrenia. Allelic associations were also observed between both Brain Derived Neurotrophic Factor Gene Single nucleotide polymorphisms and comorbid alcohol dependence in the replication group. Haplotype analysis showed that the rs6265–rs7103411 A/C haplotype was associated with comorbid alcohol dependence (Cheah et al., 2014). Female heroin-dependent subjects with BPD had a lower frequency of the high-activity allele (L: 4 repeats [4R]) of MAOALPR when compared with those without BPD. In addition, they were found to have a higher 5-HTTVNTR 10R/10R genotype frequency than normal female controls (Yang et al., 2014). In a recent observational study, haplotypes of the rs183294 and rs209356 markers were significantly associated with history of suicide attempt as well as suicide specifier scores among individuals diagnosed with schizophrenia with suicidal behavior who had a history of alcohol abuse or dependence (Zai et al., 2014).

Most of the existing genetic studies have focused on the serotonergic and dopaminergic systems. However, the findings from individual studies remain largely unreplicated. Hence, it is difficult to draw conclusive inferences based on the existing evidence.

Studies on biomarkers/biochemicals/neuroreceptors. Growth hormone and beta-endorphin responses to clonidine are blunted among siblings of heroin-dependent subjects with personality disorders (Gerra et al., 1994). The genetic serotonergic impairment is unlikely to be involved in the pathogenesis of heroin dependence. However, it is likely to be associated with the presence of familial depression in comorbidity with heroin dependence. In addition, the GABAergic system is impaired only in heroin-dependent subjects with comorbid anxiety disorders and not among those with heroin dependence alone. Central hypodopaminergic state is associated with transient depressive symptoms observed among alcohol-dependent subjects undergoing detoxification. Subjects with alcohol dependence who commit suicide have a region-specific change in serotonin. Lifetime impulsivity and mood symptoms among subjects with alcohol dependence syndrome are associated with prefrontal cortex serotonin receptor mRNA levels (Thompson et al., 2012). Among individuals with comorbid substance use disorder and schizophrenia, improvement in substance use parameters is not associated with changes in endogenous cannabinoids. In addition, baseline anandamide levels predict endpoint substance-use-related scores among individuals with comorbid schizophrenia and substance use disorders. Monounsaturated N-acylethanolamines levels are also enhanced by comorbid mood and anxiety disorders in cocaine addicts. The magnitude of dopamine transporter blockade induced by methylphenidate in adolescents with comorbid ADHD and substance use disorders is comparable with that found in adolescents with ADHD alone (Szobot et al., 2008). Assessment of various cytokines among abstinent adults with cocaine use disorders categorized cocaine users into different subgroups with increased prevalence of comorbid psychiatric disorders (mood [54%], anxiety [32%], psychotic [30%], and personality [60%] disorders]. IL1β was increased in users with psychiatric disorders relative to those users with no diagnosis (Araos et al., 2015).

Studies on neuroendocrinology. Studies in the area of neuroendocrinology of dual disorders have focused on individuals with depressive disorders and PTSD. The comorbid substance use disorders among these individuals have included opioid dependence and alcohol use disorders. Individuals with comorbid opioid dependence and depressive disorders have distinct responses to challenge with various biochemicals that are mediated through neurochemicals such as cortisol, growth hormone, and prolactin. Elevated total triiodothyronine among individuals with PTSD is not influenced by comorbid alcohol use disorder (Karlović et al., 2004).

Limitations and Future Directions

There is limited published literature on neurobiology of dual disorders. Although the existing literature spans through various neurobiological domains, none of the comorbid substance use disorder and psychiatric disorder dyads have been studied extensively. The findings reported in individual studies remain largely nonreplicated. Hence, it is difficult to draw definitive conclusions based on findings of the published literature. Most of the studies have included relatively small sample size. Whereas a few of the studies have included female subjects and adolescents, most have included only adult men. Some of the studies have failed to include an appropriate control group. In addition, the interventional studies have failed to randomize the subjects. Diagnostic criteria for psychiatric disorders and substance use disorders also vary across the study as do the inclusion thresholds. Possible exposure to potential confounders could not be achieved in some interventional studies because of methodological limitations. The studies have made cross-sectional assessments during periods of active use or abstinence. The studies have failed to make prospective assessments over different phases of substance use. The investigations tools employed by most of

the studies have limited exploratory and precision values. For example, the neuropathological studies employed nonspecific stains that could not distinguish between the various cell types.

There is a need to study various neurobiological aspects of dual disorders in greater detail. The future studies should assess various dual-disorder dyads in greater depths using more rigorous study designs. The studies should include diverse populations with larger sample sizes. The studies conducted among independent substance use disorders and psychiatric disorders could guide the future studies on dual disorders. This shall offer a much needed comparison between populations with isolated substance use disorders or psychiatric disorders and those with dual disorders. Such information shall help make more informed decisions for individuals with dual disorders. A more detailed understanding of the neurobiological aspects of dual disorders shall offer a substrate to explore effective interventions for those diagnosed with dual disorders.

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