Review

iMedPub Journals
http://www.imedpub.com

Clinical Psychiatry

2015
Vol. 1 No. 2: 9

Psychopharmacology and Intellectual Disabilities: Towards Personalized Medicine

Dr Bruce McCreary[1] and Muhammad Ayub[2]

1 Division of Developmental Disabilities, Associate Professor, Department of Psychiatry, Queen's University, 191 Portsmouth Avenue Kingston, K7M8A6 Kingston, Canada
2 Professor Emeritus, Division of Developmental Disabilities, Department of Psychiatry, Queen's University, Kingston, Canada

Corresponding author: Muhammad Ayub

Division of Developmental Disabilities, Associate Professor, Department of Psychiatry, Queen's University, 191 Portsmouth Avenue Kingston, K7M8A6 Kingston, Canada.

ma84@queensu.ca

Tel: 1+613-549-7944

Highlights

- Optimal pharmacotherapy in treating the mental disorders seen in persons with intellectual disabilities relies on care plans formulated on a broad biopsychosocial perspective.
- An inclination for these individuals to present with behavioral features, particularly aggression, has contributed to a long-standing pattern of overuse of antipsychotic medications.
- Many jurisdictions, having closed their traditional institutions, have yet to establish the specialized secondary and tertiary mental health services needed to provide care and relevant professional training.
- Contemporary advances in genetics and neuroscience hold promise in facilitating accurate diagnosis and individualized medical interventions i.e., "personalized medicine" for these individuals.

Received: September 17, 2015, **Accepted:** November 23, 2015, **Published:** November 28, 2015

Introduction

Intellectual disability is characterized by significant limitations in both intellectual functioning and in adaptive behavior which originates before the age of 18. Intellectual functioning is measured by performing Intelligence Quotient (IQ) test. Generally, an IQ test score of around 70 or below indicates a limitation in intellectual functioning. Adaptive behavior is the collection of conceptual, social, and practical skills that are learned and performed by people in their everyday lives. Intellectual Disability is grouped into mild, moderate, severe and profound categories based on IQ level. Among adults with ID prevalence rates for mental disorders are higher than in the general population. The prevalence rate of mental disorders in general population is 30.5% but Cooper and colleagues reported a rate of 40.9% in 1,023 adults with ID. Up to 62% of adults with ID exhibit socially inappropriate behavior, so-called problem or challenging behavior. In this population challenging behavior is treated with psychotropic medication, behavioral and environmental interventions or a combination of these. The role of psychotropic medication has been questioned. We here intend to review the main issues surrounding use of psychotropic medication in people with intellectual disability [1-4].

Questionable practices regarding the use of psychotropic medications can be listed with the various controversial issues that surrounded the care of persons with intellectual disabilities in institutions during the 20th century. Like the use of seclusion rooms, physical restraints and aversive behavioural procedures, widespread use of psychotropic medications generated polarized attitudes, public misunderstanding and media attention; these contributed to diminished confidence in institutional care, and ultimately, in many jurisdictions a shift to community-based services.

Historical Background

In 1976, Sprague provided an "overview" of psychopharmacology in the USA observing that 65% of those living in institutions received psychotropic medications; there was no data for those living in the community. He reported the FDA was concerned about "heavy usage for long periods of time" [5-6].

In 1986, Aman & Singh published a critical appraisal of a series of studies on medication use at the Coldwater Regional Centre for Developmental Disabilities in Michigan. These studies suggested that antipsychotic drugs, the most widely prescribed psychotropics, actively interfered with learning, adaptive behaviour and habilitation, obviously a major concern (if replicated) in the care of persons with intellectual disabilities [6] Aman & Singh were critical of the methodologies employed in the

Coldwater studies, quoted others with findings that contradicted their results and concluded "all encompassing judgments about the value of pharmacotherapy are premature". In 1999, Nøttestad and Linaker examined the needs of individuals with intellectual disabilities for psychiatric services before and after "complete deinstitutionalization" in Norway; they concluded, "The behaviour and mental health problems of people with intellectual disability are the same as, or worse than, before reform and they receive less service" [7]. In a separate 2003 report these authors [8] described psychotropic drug use after institutionalized individuals had moved to community settings. They observed no major changes in the use of antipsychotic medications and that "challenging behaviour" was the main predictor for use of these drugs. They reported that difficulties in determining the extent to which presenting behaviours are the result of a psychiatric illness or a behaviour disorder were a continuing problem for caregivers and general practitioners. They recommended that both specialized services and extra training for caregivers and general practitioners be established.

Accordingly, it now appears clear that coexistence in an individual of intellectual disability and another mental disorder did not arise from institutional living and exists as a true comorbidity for many now living in the community. This paper reviews published information on contemporary practices in the use of psychotropic medications in managing this comorbidity, including the anticipated benefits of "personalized medicine" as it evolves in the 21st century.

Contemporary Practices

Providing care in the community for persons with intellectual disabilities includes supports and services for those with an additional diagnosis of mental illness or difficult behaviour. Assumptions that mainstream health and mental health care providers could simply add individuals leaving institutions to their caseloads are now recognized as misguided; indeed, these providers look to subspecialists for consulting assistance and new approaches to coordination of health and social services in local communities are required.

This section reviews developments in psychopharmacology as related to intellectual disabilities and mental illness since the turn of the century, including issues such as refinements in diagnosis and categorization of mental disorders, improved training for professionals and for paid caregivers, & restructured quality assurance procedures. As will be seen each of these issues can be characterized as "work in progress" with some jurisdictions leading the way and others only getting started.

The UK has been a leader in providing community-based services for persons with intellectual disabilities and mental illness, partly due to formal recognition that "learning disabilities psychiatry" is a designated subspecialty. Recognizing the problems involved in utilizing traditional approaches to diagnosis and categorization of mental disorders, in 2001 the UK Royal College of Psychiatrists published DC-LD [9]. Based on ICD-10, DC-LD sets out descriptions of mental disorders modified to accommodate the intellectual and communication impairments of persons with intellectual disabilities. It is also structured to address the challenges involved in clearly distinguishing isolated problem behaviours from those linked to medical problems or other mental disorders because those with intellectual disabilities often express subjective distress behaviourally.

Another important UK contribution is represented by the Frith Prescribing Guidelines for Adults with Learning Disability [10] published in 2005. The guidelines provide prescribers with a listing of commonly encountered clinical scenarios, algorithms applicable to selecting optimal pharmacological approaches and practical suggestions about monitoring and follow up. An international guide to prescribing psychotropic medication for management of problem behaviors in adults with intellectual disabilities was published by the World Psychiatric Association (WPA) in 2009 [11]. The guide "provides clinicians and carers of adults with ID worldwide with good practice advice despite the lack of good quality evidence on this subject". The reference to "evidence" reflects an abundance of case reports and small sample sizes and a dearth of larger, randomized and placebo controlled studies in the professional literature. The WPA guide identifies the important role of DC-LD or the DM-ID (a similar nosology based on DSM published in 2007 [12]) in formulating care plans from a comprehensive biopsychosocial perspective.

MHiLD, a model specialist mental health service that evolved in southeast London following the closure of the Darenth Park institution that served the area, provides an ideal structure for providing care, including the use of psychotropic medications. The model includes community-based clinics, specialist inpatient services and training for care providers and caregivers. These secondary and tertiary care contributions are fully documented in a 2010 Maudsley Monograph that includes attention to developments in genetics and imaging to be considered below in relation to personalized medicine and psychopharmacology [13,14].

Another perspective on medication use in the care of persons with dual diagnosis is incorporated in an evaluation of positive behavioural support from Roscommon, Ireland. The evaluation is focused on 5 individuals with severe challenging behaviours (4 aggression, 1 self injury); each has additional mental disorders (mood disorder 3, psychosis 2, autism 2). Four of the subjects were treated with psychotropic medications during the provision of behavioural interventions lasting 24 months; the individual with self injury improved with an antidepressant medication and one with aggression improved as prolactin levels decreased following withdrawal of chlorpromazine. The evaluation provides strong evidence for effective inter-professional collaboration in managing "high needs" individuals with intellectual disabilities and mental illness [15].

In 2011, an audit of the UK antipsychotic prescribing practices involving 2319 patients from 39 clinical services observed: "Most prescriptions for antipsychotic drugs in people with ID are consistent with the evidence base and the overall quality of prescribing practice, as measured against recognized standards, is good, although in some patients potentially remedial side effects may not be detected and treated." In this audit 46% of the patients received an antipsychotic drug; since 27% of the patients had a psychosis chart diagnosis, it is clear that others with autism, anxiety, agitation and aggression continue to receive

antipsychotics "off label". Seventy-nine percent of the patients included in the audit were listed as "outpatients" [16].

Finally, the challenges involved in training professionals to provide care for person with dual diagnosis appear to have received limited attention since the turn of the century. The conclusions of a unique review of 27 studies published in English since 1995 [17] are significant:

A mandatory training course for all professionals who might work in Intellectual Disability or Mental Health services is recommended.

Such training should provide opportunities for direct contact and supervised experience with individuals with co-morbid intellectual disability and mental illness.

In summary, published information on the care of persons with co-morbid intellectual disability and mental illness since the turn of the century demonstrates that neither a "normal" life in the community nor reliance on local generic health care providers can resolve the challenges faced previously in traditional institutions. The need for specialized secondary and tertiary level services is now clear and innovative interdisciplinary approaches, many developed in the UK, are being established. Use of psychotropic medications has an important continuing role.

Personalized Medicine

The term "personalized medicine" relates to a growing recognition that traditional categorizations of disease, including sections pertaining to mental disorders, are not sufficiently precise to determine the design and use of medications. With respect to mental disorders, now classified on the basis of symptomatology and natural history, the aim is to shift focus to create a new approach based on the neural networks and neurotransmitters that are malfunctioning: Once these abnormalities are clear, medications can be designed and prescribed to correct or modify them. The late Lionel Penrose astutely forecast this new direction in his 1965 Maudsley lecture, "The contribution of mental deficiency research to psychiatry": "What then, is the chief contribution which experience in mental deficiency research can offer to psychiatry? I believe it is the suspicion that the great clinical groups of traditional psychiatry, which are amplified by Kraepelin, and which still determine psychiatric teaching to a large degree, do not represent the true etiological grouping" [18]. This section explores the promise of the personalized medicine concept in resolving the continuing challenges involved in using psychotropic medications in managing those with co-morbid intellectual disability and mental illness [19].

Mefford, Batshaw and Hoffman note that genetic mutations are an important contributor to the causes of intellectual disability and autism and that next generation sequencing procedures have already moved into clinical diagnostic laboratories; copy number changes and micro-deletions have also been identified as risk factors for schizophrenia, epilepsy and ADHD [19]. Genetic factors are now recognized to influence the metabolism of psychotropic drugs; Mulsant & Lenze [20] have recently observed that while clinicians are currently unlikely to be in a position to select psychotropics based on a patient's genetic disposition "within the next decade antidepressant and antipsychotic pharmacogenetics could guide the selection of medications to avoid specific adverse effects". MacQueen [21] concludes that neuroimaging and electrophysiological techniques useful in bridging the gap between the clinical symptoms of psychiatric illness and the genomic and proteomic mechanisms that are disrupted are at an early stage, but notes that psychiatry has always trended towards personalized medicine: "The notion of tailoring treatments to specific patients is ingrained in psychiatric practice."

For some time clinicians have observed that individuals with particular ID syndromes are predisposed to certain mental disorders. For example those with phenylketonuria, in addition to severe intellectual impairment, often manifested attentional problems, autistic features and self injury; with early diagnosis and prompt treatment with a low phenylalanine diet the intellectual impairment and the features of the various psychopathologies are prevented. Early efforts to correct low levels of serotonin in person with Down's syndrome by administering tryptophan, its metabolic precursor were abandoned because of iatrogenic seizures; more recently however, tryptophan has been shown to eliminate aggressive outbursts (i.e., a "challenging behaviour") in mature individuals with this syndrome [22]. It is now known that persons with Down's syndrome are uniquely predisposed to Alzheimer's Disease in later years, thought to be related to the amyloid precursor protein gene on a triplicated chromosome #21 – amyloid is plentiful in the brain plaques of Alzheimer's Disease [23]. So, awareness of the causes of particular ID syndromes contributes to important clues about the causes of associated mental disorders, and can offer insights about how one might prevent or treat them towards personalized medicine.

A review of the developing literature on the di George syndrome, first described in 1965 and now usually referred to as the velocardiofacial syndrome [24], illustrates further how study of an intellectual disability syndrome can contribute to the development of personalized treatment. Although hypocalcemia, congenital heart disease, and palatal abnormalities are the focus of clinical attention in younger children, developmental and mental health problems emerge as they mature. Intellectual impairment, usually mild, is accompanied by attention deficit, schizotypal personality characteristics, mood problems, and by young adulthood, 25-30% of these individuals are diagnosed as psychotic. Given that schizophrenia is a major public health concern, individuals with a characteristic deletion of chromosome #22 and a rate of schizophrenia 25 x the population rate attract special attention from researchers. The gene imbalance created by the deletion suggests that the genes involved have a significant role in causing schizophrenia and as well in the causation of the mental health problems ante-dating it. Once the individual genes are identified, their role in causing neurodevelopmental and neurotransmitter abnormalities will lead to specific prevention and treatment methods towards personalized medicine [25].

Study of cohorts of individuals, with mutations either in the same gene or group of genes involved in a biological pathway, allows delineation of developmental trajectories. In turn this knowledge helps predict clinical patterns of psychopathology, natural history and provide useful information for either development of new

treatments or better applications of already available treatments. Given the overlap between etiology of ID and major psychiatric disorders study of these cohorts is likely to inform the treatment of psychiatric disorders. For example clozapine is the effective in Neuroxin 1 gene disorders; Neuroxin 1 mutations have been implicated in ID, Autism and Schizophrenia [26-28].

In summary, new developments in genetics and neuroscience are leading to revised approaches in diagnosing and categorizing psychopathology. Indeed, as predicted many years ago by Penrose, insights based on careful study of various ID syndromes can show the way to tailor-made preventive and treatment interventions, so called “personalized medicine”.

Conclusion

While excessive use of psychotropic medications appears to have contributed to loss of respect for traditional institutional care, contemporary challenges in providing optimal care for those with co-morbid intellectual disability and mental illness in local communities imply a continuing need for rational pharmacotherapy.

It is now clear that care plans for individuals with dual diagnosis are best created after a comprehensive biopsychosocial assessment. Although not fully developed in all jurisdictions, a regional tertiary care service with effective linkages to family and agency caregivers and to primary and secondary health providers is needed for success. The service provides specialized ambulatory and inpatient care and training for caregivers and professional care providers in the region served.

There is growing awareness based on genetic and neuroscience research that current approaches to diagnosis and categorization of mental disorders fail to provide an appropriate basis for rational pharmacotherapy. Examination of the psychopathology that accompanies selected ID syndromes helps in identifying patterns that reflect specific genetic and neurodevelopmental abnormalities, thereby facilitating a future for “personalized medicine”.

References

1 Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, et al. (2005) Prevalence and treatment of mental disorders, 1990 toN Engl J Med 352: 2515-23.

2 Cooper S-A, Smiley E, Morrison J, Williamson A, Allan L (2007) Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. Br J Psychiatry 190: 27-35.

3 Ballinger BR, Ballinger CB, Reid AH, McQueen E (1991) The psychiatric symptoms, diagnoses and care needs of 100 mentally handicapped patients. Br J Psychiatry Feb 158: 251-4.

4 Deb S, Thomas M, Bright C (2001) Mental disorder in adults with intellectual disability. 2: The rate of behaviour disorders among a community-based population aged between 16 and 64 years. J Intellect Disabil Res; Dec 45: 506-14.

5 Sprague RL (1977) Overview of psychopharmacology for the retarded in the United States Research to Practice in Mental Retardation III Biomedical Aspects - Google Scholar. In: Research to Practice in Mental Retardation 199-202.

6 Aman MG, Singh NN (1986) A critical appraisal of recent drug research in mental retardation: The Coldwater studies. Journal of Intellectual Disability Research 30: 203-16.

7 Nøttestad JA, Linaker OM (1999) Psychiatric health needs and services before and after complete deinstitutionalization of people with intellectual disability. J Intellect Disabil Res Dec; 43: 523-30.

8 Nøttestad JA, Linaker OM (2003) Psychotropic drug use among people with intellectual disability before and after deinstitutionalization. J Intellect Disabil Res Sep; 47: 464-71.

9 Cooper S-A, Melville CA (2003) Einfeld SL Psychiatric diagnosis, intellectual disabilities and Diagnostic Criteria for Psychiatric Disorders for Use with Adults with Learning Disabilities/Mental Retardation (DC-LD). Journal of Intellectual Disability Research. Sep 47: 3-15.

10 Bhaumik S, Branford D (2005) The Frith Prescribing Guidelines for Adults with Learning Disability. London: Taylor and Francis.

11 Deb S, Kwok H, Bertelli M, Salvador-Carulla L, Bradley E, et al. (2009) International guide to prescribing psychotropic medication for the management of problem behaviors in adults with intellectual disabilities. World Psychiatry Oct 8: 181-6.

12 Fletcher RJ, Loschen E, Stavrakaki C, First M (2007) Diagnostic Manual -- Intellectual Disability (DM-ID): A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability NADD Press.

13 Eddie Chaplin, Jean O'Hara, Geraldine Holt, Steve Hardy, Nick Bouras (2008) MHiLD: a model of specialist mental health services for people with learning disabilities. Adv Mental Hlth Learn Disabil Dec 1; 2: 46-50.

14 Bouras N, Holt G (2010) Mental health services for adults with intellectual disability: Strategies and solutions. Psychology Press.

15 McClean B, Grey IM, McCracken M (2007) An evaluation of positive behavioural support for people with very severe challenging behaviours in community-based settings. J Intellect Disabil Sep11: 281-301.

16 Paton C, Flynn A, Shingleton-Smith A, McIntyre S, Bhaumik S, Rasmussen J, et al. (2011) Nature and quality of antipsychotic prescribing practice in UK psychiatry of intellectual disability services. Journal of Intellectual Disability Research 55: 665-74.

17 Werner S, Stawski M (2012) Mental health: knowledge, attitudes and training of professionals on dual diagnosis of intellectual disability and psychiatric disorder. J Intellect Disabil Res. Mar 56: 291-304.

18 Penrose LS (1966)The contribution of mental deficiency research to psychiatry. Br J Psychiatry 112: 747-55.

19 Mefford HC, Batshaw ML, Hoffman EP (2012) Genomics, intellectual disability, and autism. N Engl J Med 366: 733-43.

20 Mulsant BH, Lenze EJ (2014) Is there a role for antidepressant and antipsychotic pharmacogenetics in clinical practice in 2014? Canadian Journal of Psychiatry 59: 59-61.

21 MacQueen G (2013) Neuroimaging and electrophysiology in predicting treatment responsiveness in depression: bridging the lab-to-clinic divide? Can J Psychiatry. 58: 497-8.

22 Bruce McCreary (2007) Tryptophan-responsive challenging behaviours in persons with Down's syndrome. Adv Mental Hlth Learn Disabil 1: 54-6.

23 Mann DM, Neary D, Testa HJ (1994)Color atlas and text of adult dementias.

24 Kapadia RK, Bassett AS (2008) Recognizing a common genetic syndrome: 22q11.2 deletion syndrome. CMAJ 178: 391-3.

25 Murphy KC (2002) Schizophrenia and velo-cardio-facial syndrome. The Lancet 359: 426-30.

26 Changasi AH, Shams TA, Pouget JG, Müller DJ (2014) Genetics of antipsychotic drug outcome and implications for the clinician: into the limelight. Translational Developmental Psychiatry.

27 Jenkins A, Apud JA, Zhang F, Decot H, Weinberger DR (2014) Identification of candidate single-nucleotide polymorphisms in NRXN1 related to antipsychotic treatment response in patients with schizophrenia. Neuropsychopharmacology 39: 2170-8.

28 Lett TA, Tiwari AK, Meltzer HY, Lieberman JA, Potkin SG, et al. (2011) The putative functional rs1045881 marker of neurexin-1 in schizophrenia and clozapine response. Schizophrenia research 132: 121-4.