TITLE

Rates of psychotropic medicine prescribing in paediatric populations in Australian general practice from 2000-2016

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RUNNING HEAD

BEACH psychotropic prescribing in paediatric patients

ABSTRACT

General practitioner (GP) prescribing of psychotropic medicines to paediatric patients is increasing across countries, sparking the need for additional research into this field. We aimed to examine prescribing rates, GP and patient characteristics and indications associated with prescribing psychotropic medicines to paediatric patients in Australian general practice, using data from the Bettering the Evaluation of Care of Health (BEACH) program. We extracted all encounters with children aged 3 to 17 years from 2000-2016, inclusive. Psychotropic medications were defined as those falling with the ATC codes N05 (Psycholeptics) and N06 (Psychoanaleptics). Of the 144,397 encounters, GPs prescribed psychotropic medicines to paediatric patients at an average rate of 1.16 prescriptions per 100 encounters (95% confidence interval 1.09-1.23). We found that psychotropic medicine prescribing to paediatric patients in Australian general practice is increasing. Particular patient characteristics (adolescent age, female, low socio-economic status and English-speaking background) were significantly associated with increased likelihood of psychotropic prescribing. GP

practices in remote or regional areas, and Australian graduate GPs were more likely to prescribe psychotropic medicines to paediatric patients. Depression, attention-deficit hyperactivity disorder, anxiety and autism were the most common psychiatric indications managed with psychotropic medicines. Antidepressants, psychostimulants, benzodiazepines, antipsychotics and other psychotropic medicines were prescribed, signifying a high rate of off-label use. Sertraline was the most common psychotropic medicine prescribed, followed by fluoxetine and methylphenidate. Future studies involving data from other prescribers, e.g. paediatricians and psychiatrists, and studies linking prescribed medicines to their indications may widen our understanding of psychotropic medicine prescribing in Australian paediatric patients.

KEY WORDS
BEACH; psychotropic medicine; off-label use; antidepressant; antipsychotic; psychostimulant

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Introduction

The use of psychotropic medicines in the paediatric population across many countries has increased in recent years (Bachmann et al., 2016; Barczyk et al., 2020; Karanges et al., 2014; Piovani et al., 2019; Varimo et al., 2020). In line with this, there are ongoing debates about the safety and efficacy of psychotropic medicines in children and adolescents, with concerns about potential unknown impacts of such medicines on the developing brain (McLaren et al., 2018). As a result of limited regulatory approvals, psychotropic medicines, including some antidepressants and antipsychotics, are often used off-label in the paediatric population for the management of psychiatric disorders (Schroder et al., 2017a; Schroder et al., 2017b). Given that paediatric patients are often excluded from clinical trials, the exposure of this population to psychotropic medicines in routine clinical practice could potentially expose them to unknown adverse events as their characteristics differ from those of the patients included in clinical trial studies (Eguale et al., 2016; McLaren et al., 2018; Wittich et al., 2012).

General practitioners (GPs) and specialists (child psychiatrists and paediatricians) generally prescribe psychotropic medicines to paediatric patients. Where deemed necessary, the management of psychiatric conditions such as depression, anxiety, attention deficit hyperactivity disorder (ADHD), schizophrenia, bipolar disorder, etc., in paediatric patients may include prescribing psychotropic medicines such as antidepressants, antipsychotics and psychostimulants, amongst other medicines (CADDRA, 2020; NICE, 2018.; NICE, 2019.; RANZCP, 2015; Taylor et al., 2018b). Differences across countries in the approval and availability of psychotropic medicines for use in paediatric patients and prescribing differences between physicians could reflect potential variations in the management of psychiatric disorders in this population (Tanana et al., 2021).

In Australia, GPs often provide primary medical care to paediatric patients and decide whether further referral to a specialist is required. A study examining the trends in the range and number of psychological problems presented to GPs in Australia highlights the increasing involvement by the GP in mental health management (Charles et al., 2011). In line with this, psychotropic medications are increasingly being prescribed by GPs to paediatric patients in Australia (Klau et al., 2021). However, while studies have indicated that GPs are involved in paediatric mental health management in other countries such as the United States, United Kingdom, Ireland and Denmark (Kaguelidou et al., 2020; McNicholas et al., 2014; Rani et al., 2008), there is still a lack of research around prescribing of psychotropic medicines to paediatric patients in general practice.

In Australia, dispensing data from the Pharmaceutical Benefits Scheme (PBS) or repatriation pharmaceutical benefits scheme (RPBS), as well as a retrospective cohort study looking at both PBS/RPBS and private prescriptions by GPs to paediatric patients have determined an increase in the prescribing of psychotropic medicines to children and adolescents (Karanges et al., 2014; Klau et al., 2021). It is important to note that psychotropic medicines may be used for various indications, both on-label and off-label, which may not always be for psychiatric indications. For example, the tricyclic antidepressant amitriptyline is approved by the Therapeutic Goods Administration (TGA) to manage nocturnal enuresis in paediatric patients (Endep, 2021), but is not approved for the treatment of paediatric depression. There appears to be a deficiency in research looking at the indications managed with psychotropic medicines in the paediatric population, indicating a lack of understanding of the extent of use of psychotropic medicines in this population.

There is a clear need for further studies looking into psychotropic medicine prescribing to paediatric patients in general practice. Thus, this study aims to examine prescribing rates, GP and patient characteristics and indications associated with prescribing psychotropic medicines to paediatric patients in Australian general practice, using data from the Bettering the Evaluation of Care of Health (BEACH) program.

Experimental Procedures

This study analysed data from the BEACH program, a continuous, national, cross-survey of Australia general practice activity, which operated from 1998 to 2016. In brief, a random sample of about 1,000 registered to practise GPs from across Australia completed the BEACH project each year. Each GP recorded details for 100 consecutive encounters on structured paper forms with consenting patients (Harrison).

Details recorded about the encounter included patient characteristics, up to three reasons for encounter, up to four indications managed, and all clinical actions taken by GPs to manage the indications. Each management action was explicitly linked to the specific indication or diagnosis managed. Management actions included medications (inclusive of prescribed, supplied and advised for over-the-counter purchase), therapeutic procedures, clinical treatments, referrals, pathology and imaging tests ordered.

Patients' reasons for encounter, indications or diagnoses managed and non-pharmacological management actions were coded according to ICPC-2 PLUS, an interface terminology classified to the International Classification of Primary Care-Version 2 (ICPC-2) (WHO, 2003). The Anatomic Therapeutic Chemical (ATC) classification was used to classify medications among recorded management details (WHO, 2021). The Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) was used to record patient relative socioeconomic status based on patient residential post code (ABS, 2018). GP practice location was classified using the Australian Statistical Geography Standard (ASGS) (ABS, 2021). Due to the low numbers of patients, we grouped Outer regional, Remote and Very remote together into one group called Outer regional/Remote. Patient language background was determined by whether the patient spoke a language other than English at home. Patient Indigenous status was determined by whether they self-identified as Aboriginal and/or Torres Strait Islander. Other patient characteristics recorded include sex, age and Health Care Concession Card (HCC) status. Reported GP characteristics include sex, age, and country of graduation.

We analysed data from April 2000 - April 2016 inclusive. We extracted all encounters with children aged 3 to 17 years inclusive. Psychotropic medications were defined as those falling with the ATC codes N05 (Psychleptics) and N06 (Psychanaleptics).

The BEACH study has a single stage cluster design, with each GP (the unit of sampling) having 100 patient encounters (the unit of inference) clustered around them. We adjusted for this cluster in all our analyses using survey procedures in SAS V9.4 to create robust 95% confidence intervals. When comparing point estimates, statistical difference was determined by non-overlapping 95% confidence intervals, which is a far more conservative estimate than the usual alpha of 0.05. A multiple logistic regression was performed on all patient and GP characteristics collected to determine the independent variables associated with the prescription of a psychotropic medication for a child using SAS surveylogistic, which also took into account the cluster design of the study.

Results

Rates of psychtoropic medicine prescribing

Of the 144,397 encounters in the BEACH data set between the years 2000 to 2016, GPs prescribed psychotropic medicines to paediatric patients at an average rate of 1.16 prescriptions per 100 encounters (95% confidence interval (CI) from 1.09-1.23). The rate was lowest in 2007-2008 (0.80, 95% CI 0.57-1.02) and highest in 2014-2015 (1.8, 95% CI 1.46-2.23) (Fig 1). Paediatric patients were

3.5% more likely to be prescribed a psychotropic medicine with each additional year in the BEACH study (adjusted OR=1.035; 95% CI 1.02-1.049) (Table 1).

GP and patient characteristics

Certain patient characteristics were associated with an increased likelihood of psychotropic medicine prescribing (Table 1).

Females compared to males were more likely to be prescribed a psychotropic medicine (OR 1.12; 95% CI 1.00-1.24).

Adolescents (aged 13-17 years) were almost 20 times more likely to be prescribed a psychotropic medicine than children aged 3-5 years (OR 19.66; 95% CI 14.32-26.99). Children aged 6-12 years were almost 5 times more likely to be prescribed a psychotropic medicine than children aged 3-5 years (OR 4.86; 95% CI 3.49-6.78).

Patients who held a healthcare card were almost twice as likely to be prescribed a psychotropic medicine than those who did not hold a health care card (OR 1.97; 95% CI 1.76-2.19). In parallel, patients who were most disadvantaged were more likely to be prescribed a psychotropic medicine than most advantaged patients (OR 1.19; 95% CI 1.06-1.34).

Patients from a non-english speaking background were less than half as likely to be prescribed a psychotropic medicine than patients from English-speaking backgrounds (OR 0.427; 95% CI 0.31-0.59).

There were no statistically significant differences in psychotropic prescribing between indigenous and non-indigenous patients.

GP characteristics associated with increased likelihood of psychotropic medicine prescribing included practice location and country of graduation. By comparison to major cities, psychotropic prescribing was more likely in GP practices in outer regional/remote areas (OR 1.31; 95% CI 1.09-1.57) and inner regional areas (OR 1.27; 95% CI 1.10-1.47). Additionally, overseas graduates were less likely to prescribe psychotropic medicines than Australian graduates (OR 0.78; 95% CI 0.68-0.88). There were no statistically significant differences in prescribing by GP sex or age.

Indications

Overall, psychiatric indications were the most common conditions for psychotropic medicine prescribing in the paediatric age group (3-17 years), increasing with age (Table 2). Indications differed across age groups and between genders (Fig 2-4). In the 3-5 year age group, insomnia, followed by ADHD, were most common in females (19.05% and 14.29% of total indications) while autism, followed by ADHD were most common in males (19.35% and 16.13% of total indications) (Fig 2). In the 6-12 year age group, ADHD, followed by anxiety were most common in females (22.69% and 13.45% of total indications), while ADHD followed by autism were most common in males (50.41% and 12.3% of total indications) (Fig 3). Comparatively, in the 13-17 year age group, depression was most common in both females and males (46.23% and 29.01% of total indications, respectively), followed by anxiety in females and ADHD in males (7% and 14.39% of total indications, respectively) (Fig 4).

Psychotropic medicines

A total of 57 psychotropic medicines were prescribed across 1829 prescriptions. We looked at the rate of prescribing for the top 15 psychotropic medicines prescribed (Fig 6). Additional details of the other psychotropic medicines prescribed are available in Supplementary Table 1.

Paediatric patients were most commonly prescribed antidepressants (54.67% of psychotropic prescriptions), followed by psychostimulants (12.44%), benzodiazepines (11.25%), antipsychotics (7.15%), non-benzodiazepine hypnotics (z-drugs) (0.76%) and non-stimulants (0.6%). Other psychotropic medicines (12.44%) and herbal medicines (0.88%) were also prescribed to paediatric patients. Data outlining all of the prescribed medicines constituting each medicine class is available in Supplementary Table 1.

Rates of antidepressant and antipsychotic prescribing increased with age in both males and females. Antidepressants were the most common psychotropic medicine class in both females and males aged 13-17 years, with the rate in females more than twice that of males (2354.55 and 1098.74 per 100,000 encounters, respectively) (Fig 5). Adolescent males (13-17 years) and younger (6-12 years) were prescribed psychostimulants approximately 5 times more than females in the same age groups; rates of 349.6 and 71.78 per 100,000 encounters in adolescents and rates of 403.17 and 78.66 per 100,000 encounters in children aged 6-12 years (Fig 5). Antipsychotic and benzodiazepine prescribing was more common in adolescent females than males of the same age group (rate of 466.6 and 399.54 per 100,000 encounters, respectively). In children aged 6-12 years, antipsychotics were more commonly prescribed to males than females (rate of 118.17 and 60.78 per 100,000 encounters, respectively), while benzodiazepines were higher in females (rate of 69.73 per 100,000 encounters) than males (rate of 55.61 per 100,000 encounters) (Fig 5).

Discussion

Our study builds on the findings of other Australian studies describing psychotropic medicine prescribing in paediatric primary care. Similar to the recent study by Klau et al. (2021), our study uses an Australian database which covers bothgovernment-subsidised and private prescription data. In addition, we thoroughly assessed GP and patient characteristics associated with psychotropic prescribing. To our knowledge, our study is also the first to include prescription indications associated with paediatric psychotropic medicine prescribing in Australian general practice.

The average rate of psychotropic prescriptions increased over the 16 years of the study by approximately 3.5% per year and our findings indicate that psychotropic medicine prescribing to paediatric patients is increasing in Australian general practice (Table 1). This increase in psychotropic medicine prescribing is also evident in the United Kingdom, the US, Canada, Australia, China, Japan, Taiwan and many countries across Europe (Piovani et al., 2019; Raman et al., 2018; Varimo et al., 2020; Xu et al., 2021).

We found socioeconomically disadvantaged paediatric patients to be 1.6 times more likely to be prescribed psychotropic medicines, with those who held a health care card twice as likely than those who did not. In line with our results, patients from low socioeconomic status families were more likely to have a mental health disorder (Enticott et al., 2016; Fergusson and Horwood, 2001; Lawrence D., 2015; Merikangas et al., 2009). A recent Australian study found that antipsychotics, ADHD medicines and antidepressants were more likely to be prescribed to paediatric patients in disadvantaged areas than least disadvantaged areas (Klau et al., 2021). A study in the US found that the rate of psychotropic prescribing in Medicaid-insured children was nearly twice the rate for those privately insured (Martin et al., 2002). Even more so, in France, youth from low-income households were nearly ten times more likely to be prescribed an antipsychotic than the general population (Bonnot et al., 2017). Hence there is an apparent need for increased attention and intervention in younger years to help address the risk factors associated with the increased likelihood of psychotropic

medicine prescribing and mental health disorders. Early intervention strategies, such as GP and specialist intervention and mental health screening for young children, as well as a comprehensive approach to address financial hardship among socioeconomically disadvantaged families or vulnerable patient groups, such as young/single mothers, are important in the management and prevention of mental health problems in youth (Colizzi et al., 2020; Hodgkinson et al., 2017).

Interestingly, patients from non-English speaking backgrounds were almost half as likely to be prescribed a psychotropic medicine than those with English speaking backgrounds. A study in California has indicated a link between non-English speaking individuals and lower odds of receiving required mental healthcare services (Sentell et al., 2007). A 2011 Australian national survey by Reavley and Jorm (2012) determined a link between non-English speaking backgrounds and a belief in the harmfulness of antidepressants. Furthermore, mental health stigma, poor health literacy, poor affordability, patient fear among other reasons, have provided possible explanations for reduced access to mental health services in culturally and linguistically diverse migrants (Fauk et al., 2021). While these reasons could provide an explanation for our results, further studies are warranted in order to identify and address a potential lack in mental health management in this population.

GPs practising in major cities appeared to prescribe less psychotropic medicines than those in inner regional or outer/regional remote cities in our study. This may be because people living in rural and remote areas have reduced access to specialist mental health and peadiatric services and thus may rely more on GPs for health care (AIHW, 2020). The resulting impact on patient care and outcomes, however, is unknown, warranting a need for further research.

Consistent with other studies, our results indicated that psychotropic medicine prescribing increases with age in paediatric patients (Heins et al., 2016; Karanges et al., 2014; Klau et al., 2021) and is more common in females (in particular, female adolescents), than males (Barczyk et al., 2020; Karanges et al., 2014; Olfson et al., 2013). In Australia, the prevalence of a major depressive disorder is higher in adolescents (12 to 17 years) than children (4 to 11 years) – 5% compared to 1.1% (Lawrence D., 2015). Adolescent females appear to be more susceptible to depression and anxiety than males, probably due to biological, cultural and social factors and stressors (Costello et al., 2002; Lewis et al., 2015; Merikangas et al., 2010; Saluja et al., 2004). We found that depression was the most common indication managed in adolescent females, at a rate around 1.5 times higher than adolescent males. ADHD, on the other hand, is the most prevalent mental disorder affecting Australian children, and the prevalence in children up to 14 years of age is 5.8% in males and 2.3% in females (Deloitte Access Economics, 2019). In line with this, management for ADHD dominated in males 6-12 years of age in our study, at a rate more than twice as much as females of the same age.

We found sertraline to be the most commonly prescribed antidepressant in paediatric patients, consistent with prescribing to paediatric patients in the US (Bachmann et al., 2016) and adolescent patients in France, China and Croatia (Deng et al., 2018; Marsanic et al., 2012; Revet et al., 2018). It is also the second most commonly prescribed antidepressant (in children and adolescents) in multiple Asian countries (Chee et al., 2016). Interestingly, of the most common antidepressants prescribed in our study (sertraline, fluoxetine, citalopram, escitalopram, venlafaxine, amitriptyline, fluvoxamine and imipramine), only four are TGA-approved for use in the paediatric age group, for the treatment of obsessive-compulsive disorder (OCD) or enuresis. Sertraline is approved for the treatment of OCD in paediatric patients aged 6 years and older, and fluvoxamine is approved for OCD in those aged 8 years and older, while amitriptyline and imipramine are approved for the treatment of enuresis in paediatric patients (Endep, 2021; Luvox, 2022; Tofranil, 2020; Zoloft, 2021). Understandably, psychotropic medicines, including antidepressants, are often used off-label in paediatric patients in line with prescribing guidelines, such as the Maudsley Prescribing Guidelines in Psychiatry (Taylor et al., 2018a). While our study indicated common prescribing for depression and anxiety in the paediatric population and high rates of antidepressant prescribing, further research is needed to link

individual medicines to their prescribed indications for a more detailed understanding of off-label use in the paediatric population.

Psychostimulants were the second most commonly prescribed psychotropic medicines in the paediatric age group, with methylphenidate and dexamfetamine most commonly prescribed. Our findings directly align with other Australian dispensing data for psychostimulant prescribing for ADHD in paediatric patients (Karanges et al., 2014). In Canada, Asia and European countries, methylphenidate also tends to be predominantly prescribed for ADHD (Bachmann et al., 2017; Okumura et al., 2019; Raman et al., 2018; Song and Shin, 2016). A recent meta-analysis by Piovani et al. (2019) found that the global pooled prevalence of ADHD medicines among paediatric patients aged 19 years and younger was higher than that for antidepressants (15.3% and 6.4%, respectively). While we found antidepressants to dominate, overall, in the paediatric age group (rather than ADHD medicines), it is important to note that our analysis did not include data from other prescribers. In Australia, paediatricians contribute the greatest proportion of prescriptions (including psychostimulants) to children and adolescents, followed by GPs and then child and adolescent psychiatrists (Karanges et al., 2014). Australian GPs are, however, becoming increasingly involved in treating mental health conditions in paediatric patients, which could attribute to the increases in prescribing of psychotropic medicines over time, as seen in our study (Karanges et al., 2014).

There are some limitations to this study. The data from this BEACH study concluded in 2016, so our study cannot address whether changes in the GP prescribing of psychotropic medicines to paediatric patients have changed in more recent years. Nonetheless, this study covers 16 years of data, and provides important insights, considering the limited research on paediatric psychotropic medicine use in primary care in Australian. Additionally, our study only examined prescribing in GP settings and did not include data from paediatricians and psychiatrists. It is important to note, however, that GP involvement in the management of mental health disorders and paediatric prescribing is increasing across the globe, and studies are needed to understand the impact and extent of their involvement.

In conclusion, paediatric psychotropic medicine prescribing rates in Australian GP settings have increased over the years, in line with findings from other countries. Psychotropic medicines were most commonly prescribed for psychiatric indications in paediatric patients, with depression being most common in adolescents (aged 13-17 years) and ADHD most common in younger children (aged 3-5 and 6-12 years). The most commonly prescribed psychotropic medicines were sertraline, followed by fluoxetine and methylphenidate in the paediatric population. Our findings support a high rate of off-label use of psychotropic medicines in the paediatric population in Australian primary care. Future studies linking prescribed medicines to their indications as well as comparative prescribing information including data from other prescribers, e.g. paediatricians and psychiatrists, could provide a wider understanding of the prescribing of psychotropic medicines to paediatric patients in Australia.

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Contributors

LT: Data analysis and interpretation, wrote first draft of manuscript

CH: Data extraction, data analysis and interpretation, reviewed and commented on each draft of the manuscript

PSN: Data analysis and interpretation, reviewed and commented on each draft of the manuscript

TFC: Conceived the study, data analysis and interpretation, reviewed and commented on each draft of the manuscript

Conflict of Interest

LT, CH, PSN, TFC: There are no competing interests to declare.

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