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REVIEW

ADHD as a Potential Risk Factor in Poor Antiretroviral Adherence Rates in HIV: A Brief Narrative Review and Suggestions for Future Research

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Abstract

This was a narrative review of the literature pertaining to antiretroviral adherence rates in patients with HIV, with a focus on ADHD as a potential risk for poor adherence. A connection is drawn between the cognitive symptoms of ADHD and risk factors for poor treatment adherence in HIV. Parallel associations between ADHD and poor treatment adherence in patients with diabetes are also discussed. Finally, some of the challenges in measuring medication adherence in patients with HIV are summarized. Future research may assess whether patients with comorbid ADHD and HIV have lower rates of adherence than those with HIV alone. Samples will need to be large to manage other contributing factors such as age; in our clinic, patients with HIV referred for ADHD evaluations tend to be younger than patients with HIV referred for assessment of other neurocognitive conditions. This artifact confounds attempts to compare adherence rates in patients with both ADHD and HIV versus those without, as younger age is independently associated with poorer medication compliance. Future research should also include the development of strategies to help infectious disease clinicians to measure adherence as well as the development of cognitive and behavioral strategies for improving adherence rates in patients at risk for poor medication compliance.

Keywords HIV/AIDS · Attention deficit/hyperactivity disorder · Youth · Cognition · Adherence · Anti-retroviral agents

Introduction and Review

Importance of Antiretroviral Adherence in HIV

As of 2018, there were 37.9 million people living with HIV across the world, including 1.7 million new infections that previous year (UNAIDS, 2019). With the latest antiretroviral treatments available, more people are living healthy lives with fairly normal life expectancies (The Antiretroviral Therapy Cohort Collaboration, 2017). However, for maximum effectiveness, it is important to achieve high levels of antiretroviral medication adherence. Virologic failure is less likely to occur with higher levels of adherence (Bezabhe et al., 2016), while mortality risk is increased with poorer adherence rates (Lima et al., 2009).

Optimal adherence rates are often defined as ≥ 95%, though there is evidence that adherence as low as ≥ 80% may be adequate with newer therapies (Bezabhe et al., 2016). Unfortunately, about one third of patients do not achieve optimal adherence rates (Bezabhe et al., 2016 and Lima et al, 2009).

Barriers to Antiretroviral Adherence in HIV

Many barriers to optimal antiretroviral adherence have been identified. Hinkin et al. (2004) documented that younger age (< 50 years), neurocognitive impairment, and drug abuse or dependence were all associated with lower rates of optimal adherence. Cognitive functions most associated with poor adherence were executive skills (such as divided attention and flexibility), verbal list learning and retention, and psychomotor speed. In a separate paper, Hinkin et al. (2007) found that patients actively using drugs over a six-month study period were four times more likely to have inadequate adherence rates, with stimulant drug users being at greatest risk of poor adherence. Furthermore, based on 3-day adherence rates, it appeared to be the state of intoxication,

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rather than the tendency to use drugs, that was associated with poor adherence.

Rao et al. (2012) and Gonzalez et al. (2011) found that higher levels of depressive symptoms were associated with lower rates of adherence. In addition to substance abuse, youth, and depression, Chesney (2000) cited inconvenient dosing frequency, dietary restrictions, pill burden, and side effects as possible deterrents to adherence. Similarly, through structured interview, Achappa et al. (2013) found that patients in a sample in India attributed their suboptimal adherence to multiple factors, including forgetting, cost, lack of support, depression, alcohol use, social stigma, and side effects.

Treatment adherence self-efficacy has also received attention as a predictor of optimal antiretroviral adherence. McCoy et al. (2016) reported that treatment adherence self-efficacy was significantly associated with adherence. They measured treatment self-efficacy with a series of questions regarding patients' confidence in taking their medications under various circumstances, such as with changes in routine, being busy, or with side effects. Johnson et al. (2006) likewise found an association between treatment adherence self-efficacy (using the same measure as McCoy et al.) and adherence. They also found that perceptions of positive provider interactions influenced beliefs in self-efficacy.

Interestingly, but perhaps not surprisingly, Stirratt et al. (2006) found that 19% of their sample of individuals with HIV in a serodiscordant relationship reported missing dosages of their antiretroviral medications due to concern about serostatus disclosure. Conversely, those in serodiscordant relationships with greater serostatus disclosure had better rates of adherence.

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD, HIV, and Adherence There is some preliminary evidence that ADHD may be linked to increased risk of HIV infection. For instance, among 100 young men with newly diagnosed HIV, 20% were diagnosed with ADHD based on self- and family-reported symptoms obtained through questionnaires (Kumar et al., 2014). Those patients with ADHD were also found to have lower rates of optimal antiretroviral adherence, had higher rates of substance use, and had higher rates of risky sexual behavior.

Regarding the latter, Flory et al. (2006) found that young adults with a childhood history of ADHD were more likely than a comparison group to have engaged in risky sexual behavior, including earlier initiation of sexual activity, more partners, more casual sex and more casual sex with infrequent condom use, and more partner pregnancies. A history of childhood conduct problems contributed significantly, though this did not account for all of the variance between the two groups.

Olazagasti et al. (2013) also found that adults with a childhood history of ADHD engaged in more risky behaviors than individuals without a history of ADHD. Inclusive, those with ADHD had more sexually transmitted diseases than those without a history, were also more likely to have sex by the age of 15, were more likely to have ≥ 26 sexual partners, and were less likely to use birth control in their 20′s and 30′s. Notably, the differences in risky behaviors were accounted for by the development of Conduct Disorder or Antisocial Disorder (CP/APD)—those with ADHD + CP/APD were more likely to engage in risky behaviors than those without CD/APD, regardless of ADHD history. Risk of CP/APD was higher, though, in those with ADHD than in those without ADHD.

Interestingly, there are some very preliminary data from genetic studies for a potential increased risk of HIV infection among those with ADHD. Specifically, Koutsilieri et al. (2014) reported in a review that the dopamine transporter (DAT) 10/10 genotype, which has previously been considered as a potential contributor to ADHD, is present more frequently in patients with HIV infection than in those without. The authors speculated that personality (behavioral) traits associated with the polymorphism may increase the risk of acquiring HIV.

ADHD and Cognition ADHD is a condition characterized by issues with inattention, forgetfulness, hyperactivity, and impulsivity (American Psychiatric Association, 2013). Specific cognitive skills, such as sustained attention, divided attention/flexibility, psychomotor and processing speed, and verbal list learning have been shown to be affected in individuals with ADHD (Woods et al., 2002; Cohorn & Rosenstein, 1998). In a meta-analysis, Schoechlin and Engel (2005) showed that adults with ADHD tended to have diminished verbal memory and complex attention (including divided attention), sustained attention, and working memory. Holst and Thorell (2017) also found diminished working memory in adults with ADHD. Notably, these cognitive symptoms in adult ADHD are some of the same symptoms that Hinkin et al. (2004) reported as being associated with poor antiretroviral adherence. Individuals with ADHD are also known to have difficulties with time management and planning, and this may relate to a tendency to fail to inhibit responses (i.e., impulsivity) during problem solving tasks, thus decreasing engagement in the planning aspect of the problem solving (Young et al., 2007). Similar to Young et al., Holst and Thorell (2017) found that planning and inhibition were diminished in adult patients with ADHD.

Based on the above, it makes some sense, then, that individuals with ADHD may be at greater risk of both infection with HIV and suboptimal treatment adherence. Their risk of infection may be increased due to engaging in impulsive, risky behaviors without planning. At the same

time, patients already infected may be at risk of suboptimal medication adherence due to forgetting to take medications and issues with the planning required to maintain adequate supplies of medication.

ADHD, Other Medical Conditions, and Adherence To date, there is some evidence that ADHD may impact medication adherence in other chronic medical conditions. For instance, in a large-scale epidemiological study conducted in Germany, Hilgard et al. (2017) found that young patients with co-morbid ADHD and Type 1 Diabetes had higher incidence rates of diabetic ketoacidosis compared to patients with Type 1 Diabetes without diagnosed ADHD. Those authors speculated that inattention may lead to missed insulin dosages, and impulsivity may contribute to uncontrolled eating habits.

Miller (2015) found that 774 adolescents and young adults with comorbid ADHD and Type 1 diabetes were more likely to report missing insulin dosages compared to 6,606 patients without comorbid ADHD. Related, the patients with co-morbid ADHD had higher mean hemoglobin A1c, and they had a higher incidence of diabetic ketoacidosis. Those with ADHD not receiving medication management of their ADHD also had a higher occurrence of severe hypoglycemic events.

Duke et al. (2012) found that among a sample of 64 adolescents with poorly controlled Type 1 Diabetes, 28.4% endorsed a diagnosis of ADHD. This is an incidence rate that they noted is significantly higher than the incidence of ADHD in the general population. Moreover, those adolescents with ADHD had lower scores than the adolescents without a history of ADHD diagnosis on a measure called the Diabetes Self Management Profile.

In a clinical study, six young patients with co-morbid ADHD from a population-based study of 175 patients with Type 1 Diabetes in two counties in Sweden were interviewed regarding their diabetes management (Lindblad et al., 2017). The patients reported to investigators that they experienced difficulties in creating routines for their diabetes treatment, and that issue was exacerbated by stress.

Methods and Challenges in Monitoring Medication Adherence in HIV

In the HIV studies reviewed regarding adherence in HIV treatment, methods utilized for assessing adherence rates varied. Measuring adherence can be challenging in both research and in the clinical setting. Clinicians often have to rely on patients' self-report or pill counting, but there are other emerging methods available with advancing technology.

Self-Report As stated above, clinicians often rely on self-report. Patients may be asked how many doses they missed during the previous month, week, or days. Alternatively, they may be asked more specific questions about adherence regarding forgetting, skipping due to symptoms, and carelessness (Morisky et al., 1986). Notably, the method used for obtaining self-report data can result in inconsistent data (Gao & Nau, 2000).

Pill Count Another method for assessing adherence in the clinic and in research is the pill count method. Here, the clinician or researcher can count the number of pills remaining in the patient's bottle, and compare that to the expected number of pills remaining if the patient is taking the medications as prescribed. This may be a more reliable method than self-report (Bangsberg et al., 2001), though this method requires the patient to have their pills with them for appointments. Unfortunately, too, it is possible to manipulate pill counts, such as by leaving excess pills at home before an appointment, as was found by Hugen et al. (2002)

MEMS Medication Event Monitoring Systems (MEMS) are electronic monitoring systems that utilize bottle cap tracking devices that record the dates and times that pill bottles are opened. The idea is that the bottles are opened to retrieve a dose of medication, thus providing a measure of adherence as well as timeliness. In a study by Arnsten et al. (2001), patients self-reported higher rates of adherence than indicated by their MEMS data. Moreover, the likelihood of viral suppression was better if the MEMS adherence rate was high than if self-reported adherence was high. This suggests that electronic monitoring may be a more accurate measure of adherence than self-report. Unfortunately, patients may manipulate their MEMS data by opening the bottles without taking pills as was observed in some research participants by Hugen et al. (2002).

Refill Rate A fourth, indirect set of methods for measuring adherence rates involves obtaining prescription claim/pill refills through automated pharmacy databases. These methods of using pharmacy records have been shown to provide data that more accurately reflect adherence compared to self-reporting (Stricker et al., 2014). Various options include, but are not limited to, determining the medication possession ratio (proportion of days the supply is obtained during a specified time period), medication gaps (the proportion of days without medication), and refill adherence (e.g., refill rates) (Andrade et al., 2006).

At our facility, we have access to the pharmacy data base, which utilizes a measure called the Parkland Score for Adherence to Medication (PSAM). PSAM uses a proportion of days covered (PDC) method, tracking availability of a prescription on a day-to-day basis, and compares it to the total number of days a patient has been on that prescription while taking hospital stays, early prescription refills, and migration between medications within the same therapeutic class into account. The PDC method is the preferred method of the Pharmacy Quality Alliance for measuring adherence rates in chronic conditions (Pharmacy Quality

Alliance, 2018). One shortcoming is that adherence rates could potentially be underestimated in one time period and overestimated in another in that delayed dispensing in one period could be counterbalanced by early dispensing in another period (Raebel et al., 2013). Another issue specific to the PDC is that oversupplies are truncated (Raebel et al., 2013).

Among patients seen in our clinic from 2017 through 2019, only 8 of 24 patients diagnosed with HIV and comorbid ADHD reported less than perfect adherence rates during appointments with providers, and one of those 8 still reported 98% adherence. Only three reported being adherent less than 80% of the time. Among 26 patients with HIV without known ADHD, only 3 reported less than perfect adherence. None reported adherence rates below 80%. In those same groups, the PSAM adherence rates were available for 36 patients (16 in the HIV + ADHD group and 20 in the HIV group). The remaining patients were either flagged by PSAM as having "insufficient data" or they were under the care of another facility (another hospital system or a nursing home where medications were managed for them). The average refill rate (PSAM) for the combined sample was only 73.05% (SD = 22.70). 10 patients' PSAM ratings were ≥ 90%, and 16 were ≥ 80%. These data suggest, then, that patients' self-reported treatment compliance may be over-inflated in comparison to more objective measures of adherence.

With regard to the issue of ADHD and adherence, in the above sample, 4 of the 16 patients with HIV and co-morbid ADHD had PSAM refill rates ≥ 80% and 12 of the 20 patients with HIV alone had PSAM refill rates ≥ 80% (see Cassill et al., 2020). Unfortunately, we could not draw conclusions based on these data regarding ADHD as a risk for poorer compliance as the ADHD sample was significantly younger than the non-ADHD group, and younger age was significantly related to poorer refill rates. This association between youth and poorer compliance was also found, as noted above, by Hinkin et al. (2004) and Chesney (2000).

Discussion

This brief, narrative review of the literature suggests that ADHD could be a risk factor for inadequate antiretroviral medication adherence in patients with HIV. While this is still a relatively new area of investigation, suboptimal antiretroviral medication adherence may be more likely in patients with HIV and comorbid ADHD. Related, ADHD has been associated with cognitive issues that have also been linked to poor medication adherence in HIV, and substance abuse has been linked to both poorer medication adherence and ADHD. There is also evidence in the literature that ADHD is associated with poorer treatment adherence in Type 1 diabetes, another chronic and life-threatening health condition.

For various reasons, there is sometimes skepticism about the diagnosis of ADHD, particularly among adults. Some concerns include the risk that individuals may be seeking evaluation of ADHD symptoms solely for the purpose of obtaining accommodations on high-stakes examinations, or that individuals are seeking prescriptions for stimulant medications to be used recreationally or sold on the black market. However, it is important to balance these concerns against the risk of missing the opportunity to diagnose and treat a potentially serious condition that can impact health and safety.

If a link between ADHD and suboptimal antiretroviral adherence can be established definitively, it could provide a tool for infectious disease specialists to be on alert for increased risk of poor treatment compliance among their patients with HIV and comorbid ADHD. Likewise, psychiatrists, neuropsychologists, and other specialists evaluating or treating patients with ADHD may be more vigilant to the risk of poor antiretroviral adherence among their patients with comorbid HIV.

Future Directions

In order to more firmly establish a link between ADHD and poor antiretroviral adherence, it will be important to obtain diagnostic groups that are matched on age, or to limit studies to those in the younger adult age ranges. This will enable researchers to identify ADHD as a risk factor independent of age with regard to treatment compliance. As noted above, youth is a risk factor for poor adherence rates.

Research should also continue to focus on the reliability of measurements evaluating antiretroviral medication adherence. Being able to reliably assess adherence allows specialists to initiate discussions with their patients when the rates are below 100%. Self-reports of adherence rates have been shown to be unreliable. The PSAM, discussed in this review, is a new and valuable tool for clinicians at our facility to monitor patients' adherence based on refill rates. However, perfect refill rates do not guarantee that patients are taking medications as prescribed. Likewise, less than perfect refill rates may not accurately reflect compliance rates. In future studies, it would be helpful to prospectively review refill rates with patients to determine whether there are reasons for less than perfect rates. Future studies may also utilize multiple external/objective measures of adherence in addition to self-report in order to continue to evaluate the relative reliability and validity of each method.

Finally, continued development of intervention strategies should also be a target of future research, including the development of tools and methods for improving adherence rates. These tools and methods may target the symptoms

of ADHD, such as forgetfulness, poor task completion, and difficulties with planning and time management. Such tools may include technology (e.g., interactive phone apps with two-way communication between patient and clinical staff) and both individual and group, face-to-face interventions aimed at helping patients implement compensatory strategies. Sanchez et al. (2006) reviewed behavioral treatment programs aimed at improving diabetes management in children. They detailed two young patients with Type 1 Diabetes with co-morbid ADHD who were able to improve frequency and consistency of self-management behaviors. Their behavioral program included the teaching of organizational skills, cued recall procedures, daily logs, and rewards. One patient was taught to use a Palm Pilot for timed reminders to complete treatment components. These same methods may be modified and applied to young adults with HIV and co-morbid ADHD to improve medication adherence and enhance behaviors to mitigate risk of infecting others due to unsafe sex or needle sharing.

Conclusion

The literature reviewed suggests that further research into the impact of ADHD on antiretroviral medication adherence rates among patients with HIV is warranted. Such research may shed light on an aspect of functioning that interferes with optimal adherence and, thus, disease control. Being able to identify a particular diagnostic group, such as those with ADHD, as potentially requiring additional supports could be valuable in improving outcomes.

Declarations

Conflicts of Interest/Competing Interests There are no conflicts of interest to report.

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