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Neuropsychiatric side effects described by patients using bictegravir with metric itabine/tenofovir alafenamide

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Abstract

The integrase-inhibitor bictegravir combination antiretroviral therapy (ART) Biktarvy became available in Australia in October 2018.Neuropsychiatric adverse drug reactions (ADRs) are associated with bictegravir and may affect persistence and adherence to treat-ment. The aim of this study was to describe the type and frequency of reported neuropsychiatric reactions in people dispensed Bik-tarvy.Ethicsapprovalwas obtained from Alfred Hospital EthicsCommittee (Project No. 541/20). Datawere collected from recordsof people dispensed Biktarvy between October 2018 and May 2020 and who subsequently had a new neuropsychiatric reactionreported to the organisation's ADR Review Committee. Data were sourced from ADR reports, medical and dispensing records, andincluded demographics, medical history, and concurrent medicines with known psychiatric adverse reactions. Data were analyseddescriptively. Biktarvy was dispensed to 1265 patients. Twenty-two (1.7%, 95% confidence interval [CI] 1.0–2.5%) people reported 50neuropsychiatric ADRs, including abnormal dreams (*n* = 13), sleep disorders (*n* = 5), and headaches (*n* = 5). The median time frominitiation to reaction was 13 (interquartile range [IQR] 4–94) days. Eighteen patients discontinued Biktarvy (1.4%, 95% CI 0.85–2.24).There was no statistically significant difference in discontinuation of Biktarvy between people who did or did not have a pre-existingpsychiatric diagnosis (p = 0.58). Concurrent medicines with known psychiatric adverse reactions were used by 10 people. A low rateof reported neuropsychiatric ADRs lead to discontinuation of Biktarvy, similar to rates in Biktarvy trials. This study adds to thepost-marketingsurveillancedataofBiktarvytoleranceamongstpeoplelivingwithhumanimmunodeficiencyvirus(HIV).

Keywords:adversedrugreactions,bictegravir,anti-infectives,neuropsychiatricadverseeffects,antiretroviral.

INTRODUCTION

First-linetherapyfortreatmentnaïveAustralianswithHIV-1 is an integrase inhibitor-based regimen.[1]Optionsfor this regimen include a combination tablet consistingof bictegravir, tenofovir alafenamide, and emtricitabine(Biktarvy), which became available in Australia in October2018toalimitednumberofpeopleprior tolistingonthePharmaceuticalBenefitsScheme(PBS)on1March 2019. Biktarvy provides an advantage over existingtreatmentoptionsduetothesingletablet combinationtherapy,oncedailydosingandnorequirementforHLA-B*5701testingpriortoinitiation. Adherenceandpersistencetoantiretroviraltherapyisessentialtoreducethetransmission,morbidity,andmortalityofHIV.[3,4]Persistencecanbeaffectedbyadversereactions.[5]Biktarvydiscontinuationratesfromneuropsychiatricadversereactionsintheinitialrandomisedcontrolledtrials(RCTs)werereportedtobe0–1%.[6–9]Neuropsychiatricadversereactionsappeartobeassociatedwiththeintegrasestrandtransferinhibitorclassandhavebeenmorefrequentlyassociatedwithdolutegravir.[10]Neuropsychiatricadversereactionsidentifiedintheoriginaltrialsfor Biktarvyincludedheadacheandinsomnia.[6–9]Post-marketingevidenceindicates,however,thatneuropsychiatricreactionsmaybeofgreaterconcernwithBiktarvy.[11]This study aimed to investigate the frequencyandnatureofneuropsychiatricadversereactionsreportedinpeopledispensedBiktarvy.

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METHOD

Setting

Thisretrospectivestudywasconductedatatertiaryreferral health service in Melbourne, Victoria, Australiathatprovidesstate-wideHIVservices.Thepharmacyservices at two different locations within our organisa-tion dispense antiretroviral medicines to people livingwithHIVunderthecareofourorganisationandshared-carespecialistgeneralpractitioners(GPs).

Clinicians at our organisation are actively encouraged toreport potential adverse drug reactions (ADRs) using theorganisation's reporting system. Patients' experience oftreatmentisreviewedateveryconsultationandoncollection ofdispensedmedicines.Reportedreactionsaredocumented on an ADR report form by a health professionaland forwarded to the Medication Safety pharmacist. TheADR report captures demographics and reaction detailsincludingdateofonset,suspectedmedicine/s,description of events and reaction/s, management, and outcome ofreaction. As part of the fortnightly review by the institu-tion's multidisciplinary ADR review committee comprisingmedicalclinicians(clinicalpharmacology,dermatology, infectious diseases, and allergy specialists)and pharmacists (medication safety, medicines information,andclinicalspecialists),causalityisascertainedbytheapplication of the Naranjo scale and assigned as beingunlikely, possible, probable, or definite.[12]Ethics approvalwas obtained from Alfred Hospital Ethics Committee (Pro-jectNo.541/20).

InclusionCriteria

People aged 18 years and over were considered eligiblefor the study if they were dispensed Biktarvy at leastonce between October 2018 to May 2020 and had a newneuropsychiatric ADR report submitted prior to October2020. A neuropsychiatric ADR was defined as either anervoussystemdisorderorapsychiatricdisorder,asclassifiedintheMedicalDictionaryforRegulatoryActivities.[13]

Outcomes

The main outcome was the reported incidence of neuropsychiatric symptoms. We also considered pre-existingpsychiatricdiagnosesandconcurrentmedicines,andfurtherreviewedwhether peoplecontinuedtreatmentwithBiktarvyafterexperiencinganeuropsychiatricADR.

DataCollection

Data from the ADR report, pharmacy dispensing system(iPharmacy[DedalusGlobal,Milan,Lombardy, Italy])andmedical records were collated using REDCap (ResearchElectronicDataCapture[Vanderbilt,Nashville,TN,USA])software. Where people accessed shared-care with a GP,missing information was obtained directly from the GP.ADR details were extracted, including the date of onset,symptom description, and management. Medical recordswereusedtoidentifyrelevantmedicalhistory,theantire-troviral regimen used prior to Biktarvy and past adversereactions to antiretrovirals. Concurrent medicines werecollated from each source to create a best possible medi-cine list, and the product information for these was used toidentifyknownpsychiatricadversereactions.

DataAnalysis

Descriptive statistics were used to determine frequencyof neuropsychiatric ADRs and describe patient charac-teristics. Fisher's exact test was used to compare proportionsforratesofdiscontinuationand95%confidenceintervalswerecalculatedforproportions.

RESULTS

Therewere1265peoplewhohadBiktarvydispensedfromthetwodispensingsites.AnADRwasreportedfor 35 (2.8%) people, of whom 22 (1.7%, 95% confidenceinterval [CI] 1.0–2.5%) experienced at least one neuro-psychiatric symptom, with a combined total of 50 neuropsychiatricsymptomsreported.Themediantimefromcommencementof BiktarvytoADRemergencewas 13 (interquartile range [IQR] 4–94) days. One person who had a severe reaction presented to the emergencydepartment;nonerequiredhospitalisation(Table1).

Most people had a combination of symptoms. Abnormaldreamswerethemostfrequentlyreportedneuropsy-chiatricadversereaction(n = 13),followedbysleepdisorders (n = 5), and headaches (n = 5). Less frequentlyreportedneuropsychiatricadversereactionsincludedamnesia, suicidal ideation, depression, fear, somnolence,panicattack,neurocognitiveimpairment,paranoia,anddecreasedlibido.Onepersonwhoexperienceddepressed mood (in conjunction with other

symptoms)hadapastmedicalhistoryofdepressionan danotherper-

Table1Characteristicsof22peoplewithreportedneuropsychiatricadverseeventstoBiktarvy

Variable	*n*(%)(unless specified)
Male	21(95.5%)
Female	1(4.5%)
AgeattimeofADR(median[IQR])	49.3 years [40.4–55.8]
YearofHIVdiagnosis(*n*=19) (median[IQR])	2007[2002–2013]
HIVcareprovidedbyhealthnetwork	9(41%)
HIVcareprovidedbyGP	13(59%)
Treatmentnaïve	1(4.5%)
Treatmentexperienced	21(95.5%)
PastADRstoantiretrovirals	3(13.6%)
Relevantpastmedicalhistory	(*n*=17)[1]
Bipolardisorder	1(5.9%)
Depression	8(47.1%)
Anxiety	5(29.4%)
Addictionsandsubstancemisuse	2(11.8%)
Nilpsychiatryhistory	6(35.3%)
ConcurrentmedicineatthetimeofADR reporting	(*n*=17)[1]
Cardiovascular	2(11.8%)
Antidepressants	7(41.2%)
Antipsychotics	3(17.6%)
Moodstabiliser	1(5.9%)
Anxiolytics	2(11.8%)
Other	3(17.6%)
Nilmedicines	7(41.2%)
AntiretroviralregimenpriortoBiktarvy	(*n*=21)
DTG/TAF/FTC	4(19%)
RAL/TAF/FTC	2(9.5%)
RPV/TAF/FTC	1(4.8%)
EVG/COBI/TAF/FTC	5(22.7%)
DRV/COBI/RPV/TAF/FTC	1(4.8%)
EVG/COBI/TDF/FTC	1(4.8%)
EFV/TDF/FTC	1(4.8%)
NVP/ABC/3TC	3(14.3%)
NVP/ZDV/3TC	1(4.8%)
NVP/TAF/FTC	2(9.5%)

3TC = lamivudine; ABC = abacavir; ADR = antiretroviral therapy; COBI = cobicistat; DTG = dolutegravir; DRV = darunavir;EFV=efavirenz;EVG=elvitegravir;FTC=emtricitabine; GP=generalpractitioner;HIV=humanimmunodeficiencyviruses;IQR=interquartilerange;NVP=nevirapine; RPV=rilpivirine;RAL=raltegravir;TAF=tenofoviralafenamide;TDF=tenofovirdisoproxilfumarate;ZDV=zidovudine.[1]Miss

a past medical history of substance (amphetamine) use.Amongstpeoplewhoexperiencedneuropsychiatric symp-toms, eight people also experienced non-neuropsychiatriceffects, specifically those that affected the gastrointestinal(nausea,diarrhoea,abdominalcramps; *n*=5),metabolic

sonwhoexperiencedabnormaldreamsandparanoiah ad

Table2ADRcausalityandseverityrating*n* = 22

ADR causalityassessmentusingtheNaranjoalgorithm[12]	*n*(%)
Probable	12 (54.5%)
Possible	10 (45.5%)
ADRseverityrating	
Mild	4 (18.2%)
Moderate	16 (72.7%)
Severe	2 (9.1%)

(weight gain; *n* = 2), and musculoskeletal (myalgia; *n* = 1)systems.

Fourteen (64%) people had recovered at the time theADR report was submitted. There were six people whohadnotrecoveredatthetime,reportingparasomnias(*n* = 5)andheadache(*n* = 1).Theoutcomewasunknownfortheremainingtwopeople, whobothreportedexperiencingsleepdisorderswithabnormaldreams.

ADRreviewfoundneuropsychiatricreactionswereeither 'possible' or'probable'causally-relatedtoBiktarvyandwerereportedtotheTherapeuticGoodsAdministration (TGA). The majority (81.8%) were classifiedasmoderateorseverereactions(Table2).[14]

ContinuationwithBiktarvy

FourpeoplecontinuedBiktarvytreatmentafterexperiencing neuropsychiatric symptoms. For those peo-ple

who continued, the reported ADRs were abnormaldreams(n = 3),nightmares(n = 2),andoneofeachparanoia,somnolence,andlethargy.Eighteenpeopleceased Biktarvy, providing a population discontinuationrate, due to neuropsychiatric adverse reactions, of 1.4%(95%CI0.9–2.2%).Thesepeopleexperiencedacombined42neuropsychiatricsymptomsthatincludedabnormal dreams (n = 10), sleep disorders (n = 5), andheadache(n = 5),aswellasanxiety,depression,anddepressedmood(n =6).

Apre-existingdiagnosisofatleastonepsychiatricmedical condition was identified in half (n = 11) and noprior history identified in one-quarter (n = 6) of patientsreporting neuropsychiatric symptoms. We were unabletoascertainifapre-existingdiagnosisexistedintheremainder (n = 5). The rate of discontinuation betweenpeoplewithapre-existingpsychiatricdiagnosis(81.8%,n = 9) did not differ from that of people with no pre-existingpsychiatricdiagnosis(66.7%,n=4;p=0.58).

Concurrentmedicinesassociatedwithpsychiatricsymptoms were used by 10 (46%) people at the time ofthe report (Table 1). One person had commenced rosuvastatinonemonthpriortocommencingBiktarvy;ondiscontinuation of Biktarvy the neuropsychiatric adversereactionresolved.Thispersonreportedexperiencingheadaches,myalgia,dizziness,andabnormaldreamsleading to insomnia. The other nine people had been ontheir medications for at least six months prior to com-mencingBiktarvy.

DISCUSSION

Fewer than 2% of 1265 people dispensed Biktarvyspontaneously reported neuropsychiatric symptoms to theirclinicianorpharmacist.Symptomsmostfrequentlyreportedwere abnormaldreams,sleepdisorders,andheadaches. The majority of people experiencing neuropsychiatricsymptomssubsequentlyceasedBiktarvy,suggestingtheseadversereactionsarepoorlytolerated.

Ourstudyfoundthatabnormaldreamsoccurredmorefrequentlythanheadaches,incontrasttoRCTdata. Abnormal dreams were identified in only one of282 participants in one RCT.[9]A sleep quality question-naire was included in three RCTs.[6,8,9]Headache was themost common neuropsychiatric adverse event reportedinfourRCTsofBiktarvy.[6–9]Thisdifferencemayberelated to the use of spontaneous ADR reporting in ourstudy rather than adverse reaction surveillance in RCTs,and/or patients and clinicians not reporting headache asanadversereactionofBiktarvy.

We identified that 1.4% (CI 0.9–2.2) of all people dispensedBiktarvydiscontinuedtreatmentsecondarytoneuropsychiatric ADRs. This rate is comparable to discontinuation rates associated with headaches, mood dis-orders, schizophrenia, abnormal dreams, insomnia andsleep disorders in the original phase 3 RCTs (range 0–1%).[6–9]Another single-centre, post-marketing, retrospec-tive study observed a 3.3% (CI 2.2–4.6%) discontinuationrate at six months, the majority of which were insom-nia/sleep disturbances.[11]That study found that discontinuationofBiktarvysecondarytoneuropsychiatricadversereactionswasindependentlyassociatedwithpeople with a pre-existing depression diagnosis. We didnot observe any association of a pre-existing psychiatricdiagnosiswithdiscontinuationofBiktarvy.

The main limitation of this study was the use of spontaneousADRreports.Assuch,ourabilitytoestimatethetrueincidenceofneuropsychiatricADRsislikelyanunderestimate. Direct participant interviews, prospectivesurveillance or review of medical records of the entirecohort dispensed Biktarvy may have identified furthercases. Approximately half of our cohort were primarilymanaged by a GP so ADR reports may not have beencompletedormayhavebeensubmittedelsewhere,increasing the likelihood of underestimation of the trueincidence of neuropsychiatric ADRs. The use of medicalrecords to identify relevant medical history and concur-rent medicines was reliant on adequate documentation,whichmayfurthercontributetounderestimationofassociated events. Several people who reported neuropsychiatricadversereactionsalsoreportednon-neuropsychiatric adverse reactions, which may have ledtothediscontinuationofBiktarvy.

CONCLUSION

Thisstudyfromalargecohortprescribed Biktarvyfound a low rate of neuropsychiatric adverse reactionsandacomparablediscontinuationratetoRCTs.Thisresearch adds to the real-life post-marketing data of Bik-tarvy tolerance amongst people living with HIV and hasfacilitated patient counselling about the risk of adversereactions for our clinic patients. Monitoring and report-ing of ADRs after the introduction of a new medicinehighlights areas for further research, eventually contributingtoimprovedmedicinesafety.

REFERENCES

1 AustralasianSocietyforHIV,ViralHepatitisandSexualHealthMedicine(ASHM).WhichregimentouseintheindividualwithHIVinfection.Sydney:ASHM;2019.Availablefrom<https://hivmanagement.ashm.org.au/initiation-

of-antiretroviral-therapy-in-the-treatment-naive-patient/which-regimen-to-use-in-the-individual-with-hiv-infection/>.

2 BrooksKM,ShermanEM,EgelundEF,BrothertonA,DurhamS,BadowskiME,etal.Integraseinhibitors: after10years ofexperience,isthebestyettocome?*Pharmacotherapy*2019;39:576–98.

3 PatersonDL,SwindellsS,MohrJ,BresterM,VergisEN,SquierC,etal.Adherencetoproteaseinhibitortherapy andoutcomesinpatientswithHIVinfection.*AnnInternMed*2000;133:21–30.

4 RodgerAJ,CambianoV, BruunT,VernazzaP, Collins S,vanLunzenJ,etal.SexualactivitywithoutcondomsandriskofHIVtransmissionin serodifferentcoupleswhentheHIV-positivepartnerisusingsuppressiveantiretroviraltherapy. *JAMA*2016;316:171–81.

5 DiBiagioA,Cozzi-LepriA,PrinaporiR,AngaranoG,GoriA,QuirinoT,etal.Discontinuationofinitialantiretroviraltherapyinclinicalpractice:movingtowardindividualizedtherapy. *JAcquirImmuneDeficSyndr*2016;71:263–71.

6 WohlDA,YazdanpanahY,BaumgartenA,ClarkeA,ThompsonMA,BrinsonC,etal.Bictegravircombinedwithemtricitabineandtenofoviralafenamideversus dolutegravir, abacavir,andlamivudineforinitialtreatmentofHIV-1infection:week 96resultsfroma randomised, double-blind,multicentre,phase3,non-inferioritytrial.*LancetHIV*2019;6:e355–e363.

7 DaarES,DeJesusE,RuaneP,CrofootG,OguchiG,CreticosC,etal.Efficacyandsafetyofswitchingtofixed-dosebictegravir,