Kliiniline küsimus nr 16

Kas kõigi alkoholi ja bensodiasepiine segakasutavate patsientide esmaseks raviks kasutada farmakoloogilist vs mittefarmakoloogilist ravi?

Kriitilised tulemusnäitajad: *abstinents, tagasilangus, alkoholi tarvitamise vähenemine, patsiendi rahulolu, patsiendi elukvaliteet, kvaliteetselt elatud eluaastate lisandumine, haiguse/vaegurluse tõttu kaotatud päevade arv, ravisoostumus, ravi katkestamine mistahes põhjusel, ravi katkestamine ravimite kõrvaltoimete tõttu, juhuslik alkoholi tarvitamine*

Ravijuhendid

Kokkuvõte tõendusmaterjali kvaliteedist

Käesolevates ravijuhendites leidus vähe tõendusmaterjali mitme aine koostarbimise kohta. Alkoholi ja bensodiasepiinide segasõltuvuse ravi käsitletakse analüüsitud materjalides lähtuvalt igast ainest eraldi. Segakasutuse korral tuleb rakendada mõlema aine sõltuvushäire tõenduspõhist ravi paralleelselt. Tunduvalt vähem leidub materjali, mis käsitleb alkoholi ja bensodiasepiinide segasõltuvusega patsientide ravi, kuna uuringutesse pole kaasatud mitme aine sõltuvusega patsiente. Kokkuleppel töörühmaga teostati Medinfokeskuse poolt lisaotsing eesmärgiga leida uuringuid, mis käsitleksid samaaegse alkoholi ja bensodiasepiinide sõltuvuse ravi.

Esimene medinfokeskuse otsing (rõhk bensodiasepiinidele, 06.10.2014):

Otsistrateegia 1:

SearchQueryItems found#19Search ((((((("benzodiazepine dependence") OR "benzodiazepine abuse") OR "Benzodiazepines/adverse effects"[Mesh])) AND (((alcoholism) OR "alcohol abuse") OR "alcohol dependence"))) AND (((systematic review) OR meta-analysis) OR randomized controlled trial**)** - 7 artiklit, millest 1 osutus valituks**:**

Ülevaateartikkel: Pregabalin in the treatment of alcohol and benzodiazepines dependence, Oulis P, Konstantakopoulos G, 2010.

Otsistrateegia 2: (üldisem).

Otsistrateegia, otsing läbi viidud 07.10.2014:

(alcohol dependence) AND benzodiazepine dependence)) OR ((alcohol abuse) AND benzodiazepine abuse)) OR Comorbid alcohol benzodiazepine) OR benzodiazepine alcohol dependence)) AND ((((treatment) OR management) OR pharmacotherapy) OR psychosocial treatment))) AND (((systematic review) OR meta-analysis) OR randomized controlled trial) – tulemuseks 61 artiklit, millest osaliselt relevantseid artikelid 2:

Ülevaateartikkel: Pharmacological strategies for detoxification. Diaper et al 2013

Süstemaatiline ülevaade: Denis et al, 2006 Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. Cochrane Database Syst Rev 2006, updated 2013 article has been withdrawn because substantially out of date.

Medinfokeskuse otsingu lõpptulemusena leidus vaid 1 ülevaateartikkel (Oulis 2010), mis käsitles farmakoteraapiat pregabaliiniga alkoholi ja bensodiasepiinide sõltuvuse ravis. Siiski, ka selles ülevaates kasutatud uuringutes ei olnud uuritavateks alkoholi ja bensodiasepiinide segatarvitajad vaid vastavalt kas alkoholisõltuvusega või bensodiasepiinisõltuvusega patsiendid. Medinfo otsingu tulemused kinnitavad samuti ravijuhendites kajastatud arvamust, et puudub tõendusmaterjal, mille põhjal saaks anda kindlaid soovitusi alkoholi ja bensodiasepiinide segakasutajate raviks. Soovitusi on ravijuhendites alkoholi ja bensodiasepiinide segakasutuse kohta antud, kuid põhinevad tõendusmaterjalil, mis on saadud kuritarvitava aine monokasutuse korral. Seetõttu lähtus sekretariaat tõenduspõhisuse kokkuvõtet tehes mõlema aine monosõltuvuse uuringutest: alkoholi võõrutussündroomi ja alkoholisõltuvuse ravi farmakoloogilised ja mittefarmakol. uuringud on välja toodud eelnevates EvSu-des: EvSu K5; EvSu K7,K8, K11. Allpool on ära toodud uuringud bensodiasepiinide võõrutus-ja sõltuvusravi kohta.

Kõige parema ülevaate tõenduspõhisest materjalist bensodiasepiinide sõltuvuse korral annab ravijuhend BAP 2012, mis jagab bensodiasepiinide sõltuvuse käsitluse kaheks: „terapeutilise

doosiga" bensodiasepiinisõltuvad patsiendid, kelleks tavaliselt on ärevuse ja unetuse probleemidega patsiendid, kes ei kuritarvita retseptiravimeid. Teine grupp on bensodiasepiinisõltuvad patsiendid, kes hangivad bensodiasepiine illegaalselt turult, on kaasuvalt muu aine sõltuvus ja tarbivad bensodisepiine suurtes annustes.

a) „terapeutilisi annuseid" kasutavad bensodiasepiinisõltuvusega patsiendid:

Tõendusmaterjali leidub selle populatsiooni kohta palju enam kui illegaalsete ainete tarvitajate kohta. Esmatasandi meditsiinis võib bensodiasepiinide sõltuvuse korral rakendada esmalt lühisekkumisi: nt perearst nõustab või saadab patsiendile kirja bensodiasepiini doosi vähendamise vajalikkuse kohta koos lisamaterjalidega eneseabivõtete kohta. Kui lühisekkumine osutub ebaefektiivseks, siis alustatakse järk-järgulise bensodiasepiinide vähendamisega ja mõnel juhul lisatakse psühhoteraapilisi sekkumisi muude sümptoomite (sageli ärevuse) kaasnemisel (BAP 2012). Parr et al 2008 meta-analüüsis näidati, et lühisekkumised (perearst teavitas patsienti kirjalikult 3 kuu bensodiasepiinide tarvitamise perioodi järel patsienti vajadusest bensodiasepiine vähendada) on bensodiasepiinidest loobumisel efektiivsemad kui tavaravi (routine care, mitteteavitamine) (3 RCT-d, OR = 4.37, CI 2.28–8.40) tõstes õnnestumise tõenäosuse 5% -lt 22% le. Oude Voshaar et al., 2003 ja 2006 (2 RCT-d) näitasid, et patsiendid, kes esmatasandis olid ebaõnnestunud bensodiasepiinidest loobumisel lühisekkumistega, nende korral oli järk-järguline bensodiasepiinide vähendamine efektiivsem võrreldes tavaraviga (vastavalt 51% vs 15%). 15 kuu pärast olid järk-järgulist ravi saanud patsientidest 36% bensodiasepiinidest vabad (baseerudes retsptide väljakirjutamise andmetele) ja 15% tavaravi saanud patsiendid bensodiasepiinidest vabad.

BAP 2012 ravijuhendis on viidatud Denis et al., 2006 meta-analüüsile, kus leiti, et järk-järguline bensodiasepiinide vähendamine on eelistatum järsult bensodiasepiinidest loobumisele. Sama meta-analüüs ning randomiseeritud platseebokontrollitud uuring Murphy and Tyrer et al 1991 ei leidunud oma uuringutes palju tõendust bensosdiasepiinide vähendamisel viia patsiendid üle pikatoimelisele bensodiasepiinidele. 2013 aastal teostati Denis et al., 2006 meta-analyysi up-date, mis leidis, et antud systemaatilises ülevaates sisualduv info on vananenud ning artikkel publitseerimisest eemaldatud. BAP 2012 nendib, et pikatoimelisele bensodiasepiinidele konverteerimisest aga võib abi olla, kui lühitoimelisest bensodiasepiinist võõrutamisel tekivad olulised võõrutusnähud. Siiski 2 bensodiasepiinide sõltuvust käsitlevat ravijuhendit (Drug misuse and dependence 2007 ja Turning Point 2012) soovitavad üle minna pikatoimelisele bensodiasepiinile. Tõendusmterjal selle soovituse kohta jääb ravijuhendeid lugedes ebaselgeks, pigem rõhutakse „good clinical practice" kogemusele.

Järk-järguline bensodiasepiinide vähendamine ning lisafarmakoteraapia ei ole näidanud täiendavat kasu bensodiasepiinide vähendamisel (14 uuringut, OR = 1.30, CI 0.97–1.73) (Parr et al., 2008).

Järk-järguline vähendamine + psühhoterapeutilised sekkumised:

Parr et al.,2008 meta-analüüs näitas, et psühhoterapeutilised sekkumised (relaxation training, cognitive-behavioural treat-ment of insomnia, self-monitoring of consumption and symp-toms, goal-setting, management of withdrawal and coping with anxiety.) suurendasid bensodiasepiinidest loobumist võrreldes tavaraviga (3 uuringut, OR = 3.38, CI 1.86–6.12) ja bensodiasepiinist võõrutamisel vaid järk-järgulise vähendamisega (7 uuringut, OR = 1.82, CI 1.25–2.67). Psühhoteraapia lisamine on osutunud efektiivseks ärevushäiretega ja unehäiretega patsientide korral: randomiseeritud platseebokontrollitud uuring esmatasandi arstiabis Baillargeon et al. (2003) leidis, et 77% kroonilise unetusega patsientidest loobusid bensodiasepiinide kasutamisest kui bensodiasepiinide vähendamisele oli liskas ka gurpiteraapia (KKT) võrreldes 38% patsientidega, kes said ainult bensodiasepiinide järk-järgulist vähendavat ravi (OR = 5.3, CI 1.8–16.2). Selline efekt püsis ka 1 aasta pärast. Otto et al., 1993 (RCT) leidsid oma uuringus, et paanikahäirega patsiendid, kes püüdsid bensodiasepiinidest loobuda ja said lisaks vähendamisele ka grupiteraapiat olid palju edukamad bensodiasepiinidest loobumisel võrreldes vaid bensodiasepiinide vähendamist saanud paanikahäirega patsienditega (76% vs. 25%, $p < 0.005$) .

b) Kõrge annusega bensodiasepiinide kasutajad ja/või illegaalsete ainete kasutajad:

BAP 2012: On vähe tõenduspõhist materjali täpsete soovituste andmiseks sellele patsiendi populatsioonile. Selliste patsientide korral tuleb hinnata, miks ja milleks nad kasutavad bensodiasepiine ja alternatiivsed ravivõimalused tuleks kasutusele võtta erinevate sümptoomide (nt. ärevus ja unetus) korral. Alkoholi või teiste narkootliste ainete tarvitamine tuleb välja selgitada.

Vorma et al. 2002 randomiseeritud kontrollitud uuring hindas kõrge annusega bensodiasepiinide kasutajate bensodiasepiinide järk-järgulist vähendamist koos KKT-ga võrreldes mittespetsiifilise standard võõrtusreziimiga. Mõlemas grupis olid patsiendid suutelised vähendama annust üle 50% (54% vs 59%). Patsiendid olid suutelised Bensodiasepiinide vähendatud annust hoidma terapeutilise annuse piires (Vorma et al., 2003). McGregor et al. 2003 viis läbi RCT fikseeritud järk-järgulise vähendamisega (5–10 mg reduction per day) versus sümptomitest lähtuva diazepaami vähendamise 44 statsionaaris viibival kõrge bensodiasepiini annusega patsientide hulgas. Ei olnud suurt erinevust abstinentsi määrades mõlema grupi puhul (27% järk-järgulise vähendamise korral vs. 18% sümptomitest lähtuv annustamine). Mõlemad grupid suutsid vähendada diasepaami annust 86% võrra ja keskmine diasepaami annus oli 14mg. Selline vähendatud annus säilis ka 1 kuu peale haiglast väljakirjutamist.

Kliinilises praktikas on kasutatud karbamasepiini statsionaaris bensodiasepiinidest võõrutamisel patsientidel, kellel on kaasuvalt opioidsõltuvus ja eirti neil, kes kasutavad bensodiasepiine illegaalselt. Mõned uuringud toetavad karbamasepiini kasutamist bensodiasepiinide võõrutussümptoomide kupeerimiseks (Di Costanzo and Rovea, 1992; Garcia-Borreguero et al., 1991; Schweizer et al., 1991).

Kuna tõendusmaterjali illegaalsete ainete + bensodiasepiinide kuritarvitajate ravi kohta napib, siis BAP 2012 toob välja praktilisi aspekte selle populatsiooni käsitlemiseks:

* kui bensodiasepiine muu sõltuvusega patsientidele kirjutada, siis peab olema selge raviplaan ja ravieesmärgid ning ajakava selleks.

*Kaasuvaid illegaalseid aineid tarvitavatele patsienditele tuleks kirjutada pikatoimelisi bensodiasepiine, mida väljastatakse päevadooside kaupa.

*Bensodiasepiinide võõrutamisel ei ole vajadust ühildada täpselt need bensodiasepiinide doosid, mida patsient ütleb endal olevat. Retsepti väljakirjutamisel piisab mõõdukast annusest, mis on tihti palju väiksem annusest, mida patsient ise väidab end kasutavat (Williams et al., 1996).

*Annuseid suuremad kui 30mg diasepaami päevas (või selle ekvivalendid) ei peaks kirjutama või neid tuleb ette väga harva (Department of Health, 2007).

* Kõrge annusega kasutajate puhul vähendades bensodiaspiinide annust terpaeutilise annuseni võib olla alguses üheks ravieesmärgiks kõrge relapsi ja ravist loobumise riski tõttu. (3 RCT-d: McGregor et al., 2003; Vorma et al., 2002, 2003). Kui terapeutiline doos on saavutatud ning patsient on psühhosotsiaalselt piisavalt stabiilne, järgnev bensodiasepiinide vähendamine võib toimuda.

Kokkuvõtvalt: kui on tegemist bensodiasepiinide sõltuvusega ja kaasuvalt muu uimasti tarbimisega, siis soovitatakse selliseid patsiente käsitleda eriarstiabis. Samuti soovitatakse eriarstiabis käsitleda kõrge annusega bensodiasepiinide tarvitajaid. Guideline 2007 soovitab bensodiasepiinid konverteerida diasepaamile ja siis vähendada annust iga 2 nädala tagant 10% algannusest.

Turning Point 2012:

Table 13: Outpatient dosing regimen for therapeutic benzodiazepine users (as at March 2009)

Client type/ setting	Withdrawal goal	Recommended regimen
Therapeutic users (regular dose of a long-acting benzodiazepine) in outpatient withdrawal	Reduction or stabilisation	Tapered withdrawal • Convert the patient to diazepam and reduce by 10% every 1–2 weeks • When dose is at around 5 mg, reduce by 1 mg • Provide ongoing review, support and reassurance • Manage therapeutic issues underlying the benzodiazepine dependence • Supervised pick-up of doses should be based on a management plan in conjunction with a community prescribing doctor

Table 14: Conversion table for benzodiazepine/diazepam transfer (as at March 2009)

Benzodiazepine (brand name)	Approximate equivalent to 5 mg diazepam
Alprazolam (Xanax, Kalma)	0.5 mg
Oxazepam (Serepax, Murelax)	30 mg
Clonazepam (Rivotril)	0.5 mg
Nitrazepam (Mogadon, Aldorm)	5 mg
Flunitrazepam (Hypnodorm)	1 mg
Lorazepam (Ativan)	0.5 mg

Drug misuse and deprendence 2007:

Drug	Dose
Chlordiazepoxide	15 mg
Diazepam	5 mg
Loprazolam	500 micrograms
Lorazepam	500 micrograms
Nitrazepam	5 mg
Oxazepam	15 mg
Temazepam	10 mg
Zaleplon	10 mg
Zopiclone	7.5 mg
Zolpidem	10 mg

Table 5: Approximate dosages of common benzodiazepines and Z-drugs equivalent to 5 mg diazepam

Kokkuvõte ravijuhendites leiduvatest soovitustest

Kümnest ravijuhendist seitsmes (SIGN 2003, NICE 2011, Austraalia 2009, NSW 2008, BAP 2012, APA 2006, Soome 2010) leidus infot käesoleva küsimuse kohta. Ravijuhendites on alkoholi ja bensodiasepiinide segakasutust käsitletud peatükkides „polysubstance use" ühe alagrupina, kus keskendutakse siis bensodiasepiinide sõltuvusele. Soovitused jagunevad seetõttu:

1. üldisteks - mitme aine koostarvitamist käsitlevad üldised põhimõtted, nt. soovitav nende võõrutusravi statsionaari tingimustes.

2. bensodiasepiinide kuritarvitamisest/sõltuvusest lähtuvad soovitused

APA 2006 ravijuhend väidab, et tõenduspõhist informatsiooni mitme aine koostarbimise kohta on väga vähe, mille tõttu ei saa anda ühiseid ravisoovitusi. APA 2006 ravijuhend soovitab läbi viia põhjalik patsiendi hindamine ja integreerida erinevate ainete sõltuvushäire ravis kasutatavad farmakoloogilised ja psühhosotsiaalsed raviviisid vastavalt nende tõenduspõhisusele. Mõned ravijuhendid nagu Soome 2010 ja Austraalia 2009 püüavad oma soovitustes seda ka teha. Vt.

täpsemalt allpool. Mõlemad ravijuhendid leiavad, et mitme aine koostarvitamine on sagedamini seotud kehalise, psüühilise ja psühhosotsiaalse komorbiidsusega, mida tuleb menetleda põhjaliku ja mitmekülgse raviplaaniga, sageli vajab see ravi statsionaari tingimustes, kuna mitme aine tarvitaja võõrutussündroom võib olla ettearvamatum, komplitseeritum ja on suurem risk võõrutustüsistuste tekkeks. Soome ravijuhend lubab hästi motiveeritud alkoholi ja bensodiasepiine segakasutavaid patsiente ravida ka ambul. tingimustes, kui järelvalve on tagatud. Mitmed ravijuhendid nendivad, et ravida tuleb korraga mõlema aine tarvitamist. Fikseeritud diasepaami doosiga alkoholivõõrutusravi on soovitav mitme aine segakasutuse korral. Austraalia 2009 leiab, et mitme aine sõltuvuse korral tuleb alustada selle aine võõrutusravi, millel on potentsiaalselt kõige problemaatilisem võõrutusseisund. Enamikul juhtudest on selleks alkoholivõõrutussündroom, mis vajab esmast lähenemist. Kaasuva aine võõrutust saab ennetada või minimaliseerida, kui:

- kasutada kaasuva aine asendusravi (substitution medication), nt diasepaam bensodiasepiinide sõltuvuse korral.

- lubada alkoholivõõrutusel taanduda, enne kui alustada teise aine võõrutamisega (nt. diasepaami doosi mahatiitrimine)

Kokkuvõtvalt Australia 2009 ravijuhendi ravisoovitused põhinevad ekspertarvamustel:

Recommendation	Strength of recommendation	Level of evidence
10.13 All patients with alcohol-use disorders should be screened for other substance use using quantity–frequency estimates, or through structured screening instruments such as the ASSIST questionnaire.	D	IV
10.14 Polydrug dependence is typically associated with higher levels of physical, psychiatric and psychosocial comorbidity that should be addressed in comprehensive treatment plans.	D	IV
10.15 Use of other drugs can be affected by cessation or reduction in alcohol use, and treatment plans should address use of alcohol and other drugs together.	D	IV

Recommendation	Strength of recommendation	Level of evidence
10.16 Patients undergoing polydrug withdrawal need close monitoring, increased psychosocial care, and increased medication. Consider specialist advice.	D	IV
10.17 Fixed diazepam dosing regimens are preferred for managing alcohol withdrawal in the context of other drug withdrawal, with regular review of the dosing regimen. Withdrawal scales (such as CIWA-Ar) need careful interpretation in patients withdrawing from multiple drugs, and should not be used to direct medication.	D	IV
10.18 Patients dependent on alcohol and benzodiazepines or opioids should be stabilised on substitution medications while undergoing alcohol withdrawal.	D	IV

Alcohol + opiates	Alcohol + stimulants	Alcohol + cannabis	Alcohol + benzodiazepines
Clinical profile			
Alcohol use is common among opiate users and increases risk for those with hepatitis C infection. Combined withdrawal may result in increased sympathetic stimulation increased dehydration, sleep, mood and gastro-intestinal disturbances.	The combined use of alcohol and stimulant drugs often leads to high levels of consumption of both drugs. Alcohol may be used to induce insomnia and relaxation in stimulant users. More severe and protracted withdrawal may be expected, related to consumption and anorexia.	Some users report using cannabis to self-medicate anxiety or insomnia linked to alcohol withdrawal. Combined withdrawal is likely to be associated with increased mood and behavioural disturbance.	Both substances modulate GABA function; simultaneous withdrawal can increase symptom severity and risk of seizures. The more protracted withdrawal syndrome associated with benzodiazepines may delay onset of withdrawal symptoms, and prolong withdrawal.
Treatment plan			
Consider stabilisation on buprenorphine or methadone while undergoing alcohol withdrawal. Higher benzodiazepine (diazepam) doses may be needed in lieu of opioid substitution.	Higher doses of benzodiazepines (diazepam) may be needed.	Higher doses of benzodiazepines (diazepam) may be needed.	Dependent alcohol and benzodiazepine users will need higher doses of diazepam, and consider a gradual diazepam taper.

Soome 2010 ravijuhend: alkoholi ja bensodiasepiinide segatarvitajate võõrutusel on suurem risk krampideks, mida tuleb võõrutusel silmas pidada. Alkoholi ja bensodiasepiinide segakasutajate ambulatoorne võõrutamine ja rehabilitatsioon tuleb kõne alla motiveeritud patsientide korral, kelle puhul on tagatud järelvalve. Keskmiselt 25% motiveeritud patsienditest on suutelised bensodisepiinide tarvitamise lõpetama esimesel katsel. Segakasutajate korral KKT ei pruugi olla efektiivsem vrd A-kliiniku standardraviga. Kui patsient tarvitab kõrgetes annustes bensodiasepiine, kasutamine on kontrollimatu ja varasemalt ambul. võõrutusravi on ebaõnnestunud, siis on näidustatud ravi statsionaari tingimustes. Bensodiasepiinide võõrutussümptoome saab monitoorida CIWA-B küsimustiku abil. Kui võõrutamine on korduvalt ebaõnnestunud, tuleks proovida patsient hoida jälgitud aine kasutamisel, et vältida „tänavaravimite“ kasutamist. Näiteks tehes kokkulepped apteegiga ravimi väljastamiste kohta. Karbamasepiini kasutamine võib aidata bensodiasepiinidest võõrutamisel, kuid põhjalikud uuringus selles osas puuduvad. Karbamasepiin võib kasutada ka võõrutuskrampide ennetamiseks.

BAP 2012 ravijuhend keskendub allolevates soovitustes vaid bensodiasepiinide monosõltuvusele:

Bensodiasepiinide võõrutus- ja sõltuvusravi korral on oluline hinnata kas esinevad füsioloogilised võõrutussümptomid ja sõltuvuse sündroom, et otsustada farmakoloogilise ravivajaduse üle.

<u>Soovitused bensodiasepiinide sõltuvuse “terapeutilise doosiga” kasutajate puhul:</u>

* Varajase, kerge sõltuvuse korral rakendada minimaalseid sekkumisi nagu informeerimine või perearsti poolt nõustamine.

* sõltuvuse olemasolul tuleb bensodiasepiinide annust retseptide väljakirjutamisel järk-järgult alandada.

* Patsiendile, kellel bensodiasepiini annuse vähendamise käigus tekivad problemaatilised võõrutusnähud tuleks minna üle lühitoimelistelt bensodiasepiinidelt pikatoimelistele.

* Psühhoteraapiate lisamine bensodiasepiinide järk-järgulisele vähendamisele tõstab raviefektiivsust eriti patsientidel, kellel on unehäired või paanikahäire.

* Lisaravimid bensodiasepiinide järk-järgulises vähendamises ei suurenda vähendamise efektiivsust. Siiski, antidepressantide, melatoniini, valproaadi ja flumaseniili kasutamine võib tulla kõne alla teatud patsientidel.

Soovitused bensodiasepiinide sõltuvuse kõrge annuse või illegaalse aine kasutamise puhul:

* Asendusravi ei ole soovitav patsienditele, kelle puhul on kindlad tõendid illegaalse aine tarbimise kohta, kuigi mõne puhul võib see vähendada illegaalsete bensodiasepiinide tarbimist.

* karbamasepiini võib kasutada bensodiasepiinide asemel, et kontrollida võõrutusnähtusid.

* Annused suuremad kui 30 mg diazepaami on harva vajalikud,ja see on piisav annus, et hoida ära bensodiasepiinivõõrutust, sealhulgas krampe väga kõrge annusega tarvitajate hulgas.

* Peaks rakendama bensodiasepiinide ja teiste ainete kasutamise skriinimist.

* Kõrge annuse kasutajate puhul bensodiasepiinide vähendamine terapeutilise annuse vahemikku võib olla kasulik ravieesmärk mõnede patsiendite hulgas.

* Bensodiasepiinide väljakirjutamisel tuleb teadlik olla potentsiaalsetest riskidest alkoholi ja opioidsõltuvusega patsientide puhul.

SiGN 2003 toob ainukese ravijuhendina välja bensodiasepiinide potentsiaalse kuritarvitamise ambulatoorse alkoholivõõrutuse ajal, mistõttu soovitab, et ambul. ravi oleks superviseeritud ning soovitavalt kloordiasepoksiidiga, millel on vähem kuritarvitamise potentsiaali kui diasepaamil. NICE 2011 ravijuhend annab soovituse alkoholi ja bensodiasepiinide segakuritarvitajate korral ravida aktiivselt mõlemat seisundit ja rohkem ravi ei kästile.

NSW 2008 ravijuhend peab samuti oluliseks põhjalikku patsiendi hindamist mitme aine koostarvitamise suhtes. Patsiendid võivad kasutada aineid erinevatel eesmärkidel:

- aine mõju suurendamiseks kasutatakse samal ajal sarnase efektiga aineid nt alcohol, kanep+ bensodiasepiinid.
- et vähendada ühe aine ebameelivaid toimeid teise ainega nt sedatsiooni vähendatakse stimulandi kasutamisega.
- aineid kasutatakse korda mööda teineteise võõrutussündroomi kupeerimiseks**.**

Ravijuhendite soovituste tekstid (inglise keeles)

SIGN 2003
4.3.4 MISUSE OF BENZODIAZEPINES

All benzodiazepines have a potential for misuse, but diazepam is the benzodiazepine most

associated with misuse and alcohol related fatality.

97,98

If used in community detoxification,

diazepam requires supervision to avoid misuse.

99

Chlordiazepoxide has a more gradual onset of

its psychotropic effects and therefore may be less toxic in overdose. These factors probably

contribute to chlordiazepoxide being less often misused and having less ‘street’ resale value.

D For patients managed in the community, chlordiazepoxide is the preferred benzodiazepine

NICE 2011:

Lk 141 Comorbid alcohol and benzodiazepine dependence

Benzodiazepine use is more common in patients with alcohol misuse than in the general population, with surveys reporting prevalence of around 10 to 20% (Ciraulo et al., 1988; Busto et al., 1983). In more complex patients it can be as high as 40%, which is similar to that seen in psychiatric patients. A proportion of alcohol misusers who take benzodiazepines will be benzodiazepine dependent. For some individuals, their growing dependence on benzodiazepines began when a prescription for with-drawal from alcohol was extended and then repeatedly renewed. For others the prescription may have been initiated as a treatment for anxiety or insomnia, but then was not discontinued in line with current guidelines.

7.17.8.3 For the treatment of comorbid mental health disorders refer to the relevant NICE guideline for the particular disorder, and:

● for alcohol misuse comorbid with opioid misuse actively treat both conditions; take into account the increased risk of mortality with taking alcohol and opioids together

* for alcohol misuse comorbid with stimulant, cannabis or benzodi-azepine misuse actively treat both conditions.

Service users who have been dependent on alcohol will need to be absti-nent, or have very significantly reduced their drinking, to benefit from psychological interventions for comorbid mental health disorders.

Austraalia 2009:

Managing polydrug withdrawal

Because of the potential for unexpected withdrawal severity, onset or duration, and the increased risk of withdrawal complications, clinicians should closely monitor and supervise patients undergoing withdrawal from multiple drugs. This will often require an inpatient (detoxification unit or hospital) setting.

The overlap of symptoms can complicate assessment and monitoring of withdrawal syndrome. As such alcohol or other drug withdrawal scales (such as CIWA-Ar, AWS) require careful interpretation, and should not generally be used for symptom-triggered medication regimens (such as the symptom-triggered diazepam regimen for alcohol withdrawal; see Chapter 5). Fixed diazepam dosing regimens are preferred for managing alcohol withdrawal in the context of other drug withdrawal. Clinicians need to regularly review medication regimens.

Chapter 10

Comorbidities

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Chapter 10 Comorbidities

Clinicians should carefully consider the order in which withdrawal from different drugs should be managed. The driving principle in determining the order of detoxification in a polydrug dependent person is to prioritise the substance with the potential for the most

problematic withdrawal. In most instances, therefore, alcohol will be the first drug from which to support withdrawal. Wherever possible, withdrawal from other drugs can be prevented or minimised by:

s using substitution medications (such as methadone or buprenorphine for opioid dependence, diazepam for benzodiazepine dependence, and nicotine replacement for tobacco dependence)

s allowing resolution of alcohol withdrawal before attempting withdrawal from other medications (with, for example, methadone or diazepam dose reduction).

This typically prolongs withdrawal. Alternatively, the treatment plan may involve longer-term stabilisation on the substitution medication (for example, methadone maintenance treatment). Table 10.2 provides information on specific polydrug withdrawal combinations and treatment plans.

Substitution medications are not available or routinely used for some polydrug combinations (such as cocaine, amphetamine, cannabis withdrawal). As well, withdrawal may be attempted in settings where substitution medications may not be readily available (such as custodial settings). Under these circumstances, patients may experience greater levels of withdrawal severity, such as agitation and sleep disturbance, that need close monitoring, increased supportive care, and increased doses of medication than would be routinely used for single drug withdrawal management.

It is important to discuss treatment plans with patients so they understand what is happening (for example, clarification that the dose of methadone will remain stable during withdrawal from alcohol). Negotiate with patients over the choice of medication. Some patients dependent upon short-acting benzodiazepines (such as alprazolam or oxazepam) may not be confident that diazepam will be efficacious in their withdrawal from both their benzodiazepine of choice and alcohol. Clinicians should regularly inform patients and carers about the likely course and nature of withdrawal symptoms.

It is important when managing polydrug withdrawal that clinicians set clear and consistent boundaries with patients who exhibit drug-seeking behaviours.

Soome 2010:

– Benzodiazepine intoxication (where the patient is unconscious) should be treated by flumazenil (0.25 mg i.v. repeatedly up to 2 mg, then 0.1–0.4 mg/h by infusion) [293, 294][A].
– The treatment of polysubstance abuse must be based on correct diagnosis and assessment of the severity of the state. Polysubstance use should be suspected if a heavy drinker or alcohol dependent person shows drug-seeking behaviour, if tolerance to benzodiazepines is observed during detoxification or if withdrawal symptoms appear when medication is reduced or withdrawn. An aggressive patient demanding a prescription, one obtaining prescriptions from various physicians or guilty of forging prescriptions may be a polysubstance user.
– At the clinic, a patient suspected of being a polysubstance user (intoxicated and lethargic, with incoordination or memory lapses, reduced inhibition, unpredictable or aggressive behaviour) should be given the required first aid. The patient should be assessed and referred to the emergency room, detoxification or sobering-up station. Further treatment should be ensured.
– Detoxification of a polysubstance user should include assessment of the stages of intoxicant

abuse and dependence. The severity of dependence can be assessed using the Severity of Dependence Scale (SDS) comprising five questions and with drug screens [295, 296].
– The severity of alcohol dependence can be assessed using the SADD [296] and alcohol abuse using the AUDIT [49, 297].
– The use of benzodiazepines can be assessed by urine drug screens and by monitoring serum drug levels.
– Polysubstance users have a tendency to convulsions due to alcohol and benzodiazepine withdrawal reactions. This risk needs to be considered in detoxification.
– Detoxification and rehabilitation of mixed users of alcohol and benzodiazepine should be possible under close surveillance in outpatient care, if the patient is sufficiently motivated [298, 299][C]. Around 25% of motivated patients are capable of stopping the use of benzodiazepines at the first treatment attempt.
– In motivated patients dependent on alcohol and benzodiazepines, cognitive behavioural therapy will probably not improve on efficacy of the standard methods used at A-Clinics [298, 299][C].
– If the patient uses high doses of benzodiazepines, if the use is uncontrolled or previous attempts at detoxification and rehabilitation in outpatient care have been unsuccessful, detoxification and rehabilitation should be carried out on a detoxification ward. The severity of withdrawal symptoms can be monitored using the CIWA-B form [300].
– If detoxification is repeatedly unsuccessful, an attempt should be made to commit the patient to supervised treatment instead of "street medication", for example by making a pharmacy contract.
– Use of carbamazepine support may improve the chances of success of benzodiazepine detoxification, and so may the use of valproate but there is no reliable evidence for this. Relevant studies have been performed on patients dependent on benzodiazepines only.
– Carbamazepine can also be used to prevent withdrawal convulsions [301].

BAP 2012:

LK 19 Recommendations: benzodiazepine dependence

Establishing the presence or absence of physiological withdrawal

symptoms and the dependence syndrome is important in deter-mining whether pharmacological treatment is appropriate.

Management of benzodiazepine dependence in 'therapeutic

dose' users

x└ In early/mild dependence minimal interventions such as

advisory letters, other information provision or General

Practitioner advice should be offered (A).

x└ Where dependence is established, gradual dose reduction

of prescribed benzodiazepine is recommended (A).

x└ Switching from a short half-life benzodiazepine to a long

half-life benzodiazepine before gradual taper should be

reserved for patients having problematic withdrawal

symptoms on reduction (D).

x└ Additional psychological therapies increase the effective-ness of gradual dose reduction particularly in individuals

with insomnia and panic disorder. Consideration should be

given to targeted use of these interventions (B).

x└ Additional pharmacological therapies do not appear to increase the effectiveness of gradual dose reduction.

However, use of additional pharmacotherapy such as anti-depressants, melatonin, valproate, and flumazenil should be considered on an individual basis (C).

Management of benzodiazepine dependence in high-dose and/or illicit drug users

x└ Maintenance prescribing in illicit drug users cannot be recommended on the basis of existing evidence, although it may reduce illicit benzodiazepine use in some patients (D).

x└ Carbamazepine may be used instead of benzodiazepines to control withdrawal symptoms (C).

x└ Doses greater than 30 mg diazepam are rarely necessary, and this is sufficient to prevent benzodiazepine withdrawal symptoms including withdrawal seizures in very high-dose benzodiazepine users (D).

x└ Drug screens should be monitored for benzodiazepine and other drug use (D).

x└ Reduction of high-dose use to a therapeutic dose level may be a useful therapeutic objective in some dependent users (D).

x└ Clinicians should remember the potential risks of benzodi-azepine prescribing in patients co-dependent on alcohol and/or opioids (D).

NSW 2008:

4.2.7 Poly-drug use

It is common for drug and alcohol clients to be using more than one drug at the one time. This 'poly-drug use', or hazardous use of more than one drug, is associated with increased risks and harms compared with single-drug use (187).

Clients may use multiple drugs in a variety of ways (187):

- To increase their intoxication by using different drugs with similar effects at the same time (eg. alcohol + benzodiazepines + cannabis)
- To offset the 'undesirable' effects of one drug (eg. sedation) by using an additional drug at the same time that diminishes this effect (eg. stimulant)
- To manage withdrawal by using drugs in a sequence

(rather than all at once) to regulate their withdrawal symptoms, improve mood, sleep, etc

Poly-drug use is associated with higher rates of psychiatric co-morbidity, increased risk of overdose, and risks associated with the interaction effects of different classes of drugs (187). For example, combining alcohol and heroin can fatally depress heart rate and breathing; combining amphetamines and ecstasy can result in severe dehydration, dangerously high body temperature, heart seizures and even death; and combining alcohol and amphetamines can result in dangerous amounts of the drugs being used without the client realising. (188). Additionally, withdrawal is likely to be more complicated if the client is ceasing use of several drugs simultaneously.

A comprehensive assessment of poly-drug use is essential for every drug and alcohol client presenting for treatment. This will help to highlight for the D&A professional which drugs are being used problematically, which drugs the client is abusing and which drugs are being used at the level of dependence.

D&A professionals should take extra time engaging clients with poly-drug use issues, and should assess the individual and combined effects of poly-drug use on the client. Clients with poly-drug use issues will consider each drug differently in terms of its impact on their lifestyle and potential to cause harm in their lives (187). Treatment plans need to consider this, and tailor interventions to the relative concern expressed by clients about the different drugs they are taking.

More information on the management of poly-drug use in drug and alcohol clients is available at http://www.turningpoint.org.au/library/lib_ctgs.html#7 (prescribing for drug withdrawal, and working with polydrug users)

APA 2006

Although the presence of multiple substance use disorders is the norm, there is limited research to guide clinicians on adapting the usual evidence-based clinical interventions to the treatment of individuals using more than one substance, including medication and psychosocial treatments. The best recommendation is for the clinician to do a comprehensive assessment of the patient and integrate the evidence-based treatment approaches, including pharmacological and psychosocial treatments, for each specific substance use disorder.

Viited

Ravijuhendid

The management of harmful drinking and alcohol dependence in primary care, a national clinical guideline, Scottish Intercollegiate Guidelines Network, 2003	SIGN 2003
Treatment of Alcohol Abuse, Current Care Guideline, The Finnish Medical Society Duodecim and the Finnish Society of Addiction Medicine,2010	Soome 2010
NSW Health Drug and Alcohol Psychosocial Interventions Professional Practice Guidelines, 2008	NSW 2008
Guidelines for the Treatment of Alcohol Problems, Australian Government Department of Health and Ageing, 2009	Austraalia 2009
Incorporating Alcohol Pharmacotherapies Into Medical Practice . Treatment Improvement Protocol (TIP) Series, Substance Abuse and Mental Health Services Administration, 2009.	SAMHSA 2009
Practice Guideline For The Treatment of Patients With Substance Use Disorders, 2nd Edition, American Psychiatric Association, 2006	APA 2006
Alcohol-use disorders: Diagnosis and clinical management of alcohol-related physical complications, National Institute for Health & Clinical Excellence, 2010	NICE 2010a
Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence, National Institute for Health & Clinical Excellence, 2011	NICE 2011
Department of Health (England) and the devolved administrations (2007). Drug Misuse and Dependence: UK Guidelines on Clinical Management. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive	Drug Misuse and Dependence 2007 * bensodiasepiinide käsitlemiseks lisatud
Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from The British Association for Psychopharmacology,2012	BAP 2012
Alcohol and other drug withdrawal practice guidelines,Turning Point Alcohol and Drug Centre, 2012	Turning Point 2012 *bensodiasepiinide käsitlemiseks lisatud

Viited süstemaatilised ülevaated ja RCT-d

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Detoxification refers to the safe discontinuation from a substance of dependence and is distinct from relapse prevention.Detoxification usually takes between a few days and a few weeks to complete, depending on the substance being misused, theseverity of dependence and the support available to the user. Psychosocial therapies alongside pharmacological treatments areessential to improve outcome. The dependencies considered in this overview are detoxification from opioids (with methadone,buprenorphine, α2-adrenoceptor agonists and adjunct medications), alcohol (with benzodiazepines, anti-glutamatergics andγ-aminobutyric acid (GABA)-ergic drugs), stimulants and cannabis (with no clear recommended pharmacological treatments),benzodiazepines (with dose tapering) and nicotine (with nicotine replacement therapy,	Pharmacological strategies for detoxification. Diaper et al 2013, British Journal of Clinical Pharmacology **Overview**

antidepressants and partial agonists). Evidenceis limited by a lack of controlled trials robust enough for review bodies, and more research is required into optimal treatment dosesand regimes, alone and in combination	
We review all available studies on the use of the newer anticonvulsant drug pregabalin (PGB) in the treatment of both alcohol dependence (AD) and ben-zodiazepine dependence (BD). In AD, the available evidence includes one open-label and one double-blind randomized studies, whereas in BD, only a few case reports and one open-label study are as yet available. In both condi-tions, PGB was found efficacious with significant improvement in withdrawal symptoms at the dosage ranges of 150–450 mg/day (AD) and 225–900 mg/day (BD). Moreover, its side effects were mild and transient. Despite the limited quality of the studies design, their findings suggest that PGB might constitute a novel efficacious and safe option in the treatment of both AD and BD.	Pregabalin in the Treatment of Alcohol and Benzodiazepines Dependence Panagiotis Oulis & George Konstantakopoulos **Review**
AIMS:To assess the effectiveness of current treatment approaches to assist benzodiazepine discontinuation. METHODS:A systematic review of approaches to benzodiazepine discontinuation in general practice and out-patient settings was undertaken. Routine care was compared with three treatment approaches: brief interventions, gradual dose reduction (GDR) and psychological interventions. GDR was compared with GDR plus psychological interventions or substitutive pharmacotherapies. RESULTS:Inclusion criteria were met by 24 studies, and a further eight were identified by future search. GDR [odds ratio (OR) = 5.96, confidence interval (CI) = 2.08-17.11] and brief interventions (OR = 4.37, CI = 2.28-8.40) provided superior cessation rates at post-treatment to routine care. Psychological treatment plus GDR were superior to both routine care (OR = 3.38, CI = 1.86-6.12) and GDR alone (OR = 1.82, CI = 1.25-2.67). However, substitutive pharmacotherapies did not add to the impact of GDR (OR = 1.30, CI = 0.97-1.73), and abrupt substitution of benzodiazepines by other pharmacotherapy was less effective than GDR alone (OR = 0.30, CI = 0.14-0.64). Few studies on any technique had significantly greater benzodiazepine discontinuation than controls at follow-up. CONCLUSIONS:Providing an intervention is more effective than routine care. Psychological interventions may improve discontinuation above GDR alone. While some substitutive pharmacotherapies may have promise, current evidence is insufficient to support their use.	Parr J, Kavanagh D, Cahill L, et al. (2008) Effectiveness of current treat-ment approaches for benzodiazepine discontinuation: a meta-analy-sis. Addiction 104: 13–24. **Meta-analysis**
Using a double-blind procedure, 68 patients with putative benzodiazepine dependence were randomly allocated to one of three groups given lorazepam (n = 22), diazepam (n = 23) or bromazepam (n = 23) in doses equivalent to those of the patients' original benzodiazepine. After four weeks the dosage was reduced in 25% quantities until no further benzodiazepines were taken. A total of 23 patients dropped out during the study, ten on lorazepam (one of whom committed suicide), seven on diazepam and six on bromazepam. There were few differences in withdrawal symptoms between the three groups but, despite the higher dropout rate, these symptoms were somewhat less marked in the	Murphy SM and Tyrer P (1991) A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. Br J Psychiatry 158: 511–516. **RCT**

lorazepam group. Withdrawal symptoms were greater in patients who had taken a benzodiazepine for greater than 5 years and were most marked in those with personality disorders, predominantly dependent ones.	
BACKGROUND: Long-term use of hypnotics is not recommended because of risks of dependency and adverse effects on health. The usual clinical management of benzodiazepine dependency is gradual tapering, but when used alone this method is not highly effective in achieving long-term discontinuation. We compared the efficacy of tapering plus cognitive-behavioural therapy for insomnia with tapering alone in reducing the use of hypnotics by older adults with insomnia.METHODS: People with chronic insomnia who had been taking a benzodiazepine every night for more than 3 months were recruited through media advertisements or were referred by their family doctors. They were randomly assigned to undergo either cognitive-behavioural therapy plus gradual tapering of the drug (combined treatment) or gradual tapering only. The cognitive-behavioural therapy was provided by a psychologist in 8 weekly small-group sessions. The tapering was supervised by a physician, who met weekly with each participant over an 8-week period. The main outcome measure was benzodiazepine discontinuation, confirmed by blood screening performed at each of 3 measurement points (immediately after completion of treatment and at 3- and 12-month follow-ups).RESULTS: Of the 344 potential participants, 65 (mean age 67.4 years) met the inclusion criteria and entered the study. The 2 study groups (35 subjects in the combined treatment group and 30 in the tapering group) were similar in terms of demographic characteristics, duration of insomnia and hypnotic dosage. Immediately after completion of treatment, a greater proportion of patients in the combined treatment group had withdrawn from benzodiazepine use completely (77% [26/34] v. 38% [11/29]; odds ratio [OR] 5.3, 95% confidence interval [CI] 1.8-16.2; OR after adjustment for initial benzodiazepine daily dose 7.9, 95% CI 2.4-30.9). At the 12-month follow-up, the favourable outcome persisted (70% [23/33] v. 24% [7/29]; OR 7.2, 95% CI 2.4-23.7; adjusted OR 7.6, 95% CI 2.5-26.6); similar results were obtained at 3 months.INTERPRETATION: A combination of cognitive-behavioural therapy and benzodiazepine tapering was superior to tapering alone in the management of patients with insomnia and chronic benzodiazepine use. The beneficial effects were sustained for up to 1 year. Applying this multidisciplinary approach in the community could help reduce benzodiazepine use by older people.	Baillargeon L, Landreville P, Verreault R, et al. (2003) Discontinuation of benzodiazepine among older insomniac adults treated with cognitive - behavioural therapy combined with gradual tapering: a randomized trial. Can Med Assoc J 169: 1015–1020. **RCT**
OBJECTIVE: The primary disadvantage of high-potency benzodiazepine treatment for panic disorder is the difficulty of discontinuing the treatment. During treatment discontinuation, new symptoms may emerge and anxiety may return, preventing many patients from successfully discontinuing their treatment. In this controlled, randomized trial the authors investigated the efficacy of a cognitive-behavioral program for patients with panic disorder who were attempting to discontinue treatment with high-potency benzodiazepines.METHOD: Outpatients treated for panic disorder with alprazolam or clonazepam for a minimum of 6 months and expressing a desire to stop taking the medication (N = 33) were randomly assigned to one of two taper conditions: a slow taper condition alone or a slow taper condition in conjunction with 10 weeks of group cognitive-behavioral therapy.RESULTS: The rate of successful discontinuation of benzodiazepine treatment was significantly higher for the patients receiving the cognitive-behavioral program (13 of 17; 76%) than for the patients receiving the slow taper program alone (four of 16; 25%). There was no difference in the likelihood of discontinuation success between the patients treated with alprazolam and those who received clonazepam. At the 3-month follow-up evaluation, 77% of the	Otto M, Pollack M, Sachs G, et al. (1993) Discontinuation of benzodiaz-epine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. Am J Psychiatry 150: 1485–1490.

patients in the cognitive-behavioral program who successfully discontinued benzodiazepine treatment remained benzodiazepine free.CONCLUSIONS: These findings support the efficacy of cognitive-behavioral interventions in aiding benzodiazepine discontinuation for patients with panic disorder.	
AIMS: To evaluate whether gradual benzodiazepine taper combined with cognitive-behavioural treatment is more effective than standard treatment for patients with dependence in out-patient clinics.DESIGN: A randomized, controlled clinical trial, using standard questionnaires and serum and urine tests. SETTINGS: Four public-sector out-patient clinics for alcohol and drug abusers in Helsinki.PARTICIPANTS: Seventy-six patients with benzodiazepine dependence (DSM-III-R). Patients taking high doses of the drug or with alcohol use disorders were included to obtain a subject group representative of usual clinical practice.INTERVENTION: Subjects received gradual benzodiazepine taper combined with cognitive-behavioural therapy (experimental group) or standard withdrawal treatment not scheduled by the researchers (control group).MEASUREMENTS: The outcome was measured in terms of attaining a state of abstinence or by a decrease in the dosage during the study period of up to 12 months' duration.FINDINGS: No statistically significant differences in the outcomes were observed between the groups. A total of 13% of the experimental group and 27% of the control group were able to discontinue drug use. In addition 67% of the experimental group and 57% of the control group were able to decrease the dose.CONCLUSIONS: The search continues for improved methods of helping patients with complicated benzodiazepine dependence.	Vorma H, Naukkarinen H, Sarna S, et al. (2002) Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. Addiction 97: 851–859. **RCT**
BACKGROUND: The study aimed to monitor subjects with benzodiazepine (BZ) dependence after withdrawal treatment in order to evaluate long-term outcome and predictors of remaining BZ-free. Subjects with high-dose dependence or co-occurring alcohol problems were not excluded.METHOD: Seventy-six participants in an earlier, randomized, controlled trial of outpatient BZ discontinuation were interviewed, and documents from their treatment settings obtained, along with urine and serum samples for BZ use. Long-term outcomes for a cognitive-behavioral treatment group and a treatment-as-usual group were measured. RESULTS: BZ discontinuation treatment outcomes were maintained in both treatment groups. No between-group differences were found. At the end of the study 25% of the subjects were BZ-free, and the median dose decrease from pre-treatment levels was 16.1 mg in diazepam equivalents. Subjects with pre-treatment doses exceeding 40 mg were able to maintain their doses at therapeutic levels through the follow-up. Pre-treatment low BZ dose, no previous withdrawal attempts, and high life satisfaction predicted success in staying BZ-free.CONCLUSIONS: In subjects with complicated BZ dependence, the benefits of BZ discontinuation treatment may persist, but more studies are needed.	Vorma H, Naukkarinen H, Sarna S, et al. (2003) Long-term outcome after benzodiazepine withdrawal treatment in subjects with complicated dependence. Drug Alcohol Depend 70: 309–314 **RCT**
Fixed and symptom-triggered taper methods during in-patient benzodiazepine withdrawal treatment were compared using a randomized controlled design. Forty-four benzodiazepine users seeking in-patient withdrawal treatment at two substance use treatment clinics in Adelaide, Australia were recruited. Measurements included the Severity of Dependence Scale and the SF-36. A scale comprising six items from the Clinical Institute Withdrawal Assessment Scale--Benzodiazepines (CIWA-B) was used to measure withdrawal symptoms. Participants were randomized to receive a fixed diazepam tapering regime or diazepam only in response to withdrawal symptoms (symptom-triggered group). Results showed that there were no significant differences between treatment groups in terms of withdrawal severity, duration of in-patient treatment, amount of diazepam administered, treatment attrition and benzodiazepine use at follow-up. Both groups showed a reduction in benzodiazepine dosage of 86% over the first 8 days which was maintained at 1 month	McGregor C, Machin A and White J (2003) In-patient benzodiazepine withdrawal: comparison of fixed and symptom-triggered taper methods. Drug Alcohol Rev 22: 175–180. **RCT**

post-discharge. Although there were improvements in some subscales of the SF-36 between baseline and follow-up, values were significantly below age-matched norms at both time-points. This study showed that benzodiazepine users entering treatment have relatively poor health and that symptom-triggered taper methods incorporating flexible dosing and flexible treatment duration are as effective as fixed dose taper methods for in-patient benzodiazepine withdrawal treatment.	
A double-blind study was performed to evaluate carbamazepine for the prophylaxis of benzodiazepine withdrawal syndrome in elderly patients--a controversial subject despite the extensive use of such drugs in old age. Thirty-six outpatients aged > or = 60 yrs suffering from general anxiety disorders and benzodiazepine abuse underwent gradual discontinuation of benzodiazepine therapy in two groups, one treated with carbamazepine and one with placebo. The carbamazepine-treated group demonstrated a lower incidence of withdrawal symptoms rated according to the Physician Withdrawal Check List ($p < 0.01$), better results with the Hopkins Symptom Check List (Covi cluster, $p < 0.01$) and a more markedly reduced score with the Hamilton Rating Scale for Anxiety ($p < 0.05$). Only 3 out of 18 patients in said group complained of side effects attributable to carbamazepine, which disappeared at lower dosages.	Di Costanzo E and Rovea A (1992) [The prophylaxis of benzodiazepine withdrawal in the elderly: the effectiveness of carbamazepine. Dou-ble-blind study v. Placebo.] Minerva Psychiatr 33: 301–304. **RCT**
In 18 patients with a benzodiazepine (BZD) dependency the drug was withdrawn. The dose of BZD was gradually reduced in nine of the patients, while the others were additionally treated with carbamazepine (CBZ) for a further 15 days after BZD discontinuation. Withdrawal symptoms were assessed every third day during the study period. When comparing results in both groups, a clear trend towards less severe withdrawal symptoms could be observed in the group treated with CBZ. Some of the differences were statistically significant on days 9-12 after BZD withdrawal. Fundamental withdrawal symptoms (like hypersensitivity to sensory stimuli, abnormal perception of movement, depersonalisation or derealisation) were also less severe in the group treated with CBZ compared with the group not receiving that treatment. These findings support the results of previous reports indicating a therapeutical effect of CBZ in BZD withdrawal.	Garcia-Borreguero D, Bronisch T, Yassouridis A, et al. (1991) Treatment of benzodiazepine withdrawal symptoms with carbamazepine. Eur Arch Psychiatry Clin Neurosci 241: 145–150.
Forty patients with a history of difficulty discontinuing long-term, daily benzodiazepine therapy were randomly assigned, under double-blind conditions, to treatment with carbamazepine (200 to 800 mg/d) or placebo. A gradual taper (25% per week reduction) off benzodiazepine therapy was then attempted. Five weeks after taper, significantly more patients who had received carbamazepine than placebo remained benzodiazepine free, this despite the fact that no statistically significant differences in withdrawal severity could be demonstrated. Patients receiving carbamazepine reported a larger reduction in withdrawal severity than patients receiving placebo, but only at a trend level, and only on the daily patient-rated withdrawal checklist. Eleven patients (28%) required antidepressant therapy for depression or panic when assessed at 12-weeks follow-up. The results of this pilot investigation suggest that carbamazepine might have promise as an adjunctive drug therapy for the benzodiazepine withdrawal syndrome, particularly in patients receiving benzodiazepines in daily dosages of 20 mg/d or greater of diazepam equivalents.	Schweizer E, Rickels K, Case WG, et al. (1991) Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. Arch Gen Psychiatry 8: 448–452. **RCT**
No abstract available	Williams H, Oyefeso A and Ghodse A (1996) Benzodiazepine misuse and dependence among opiate addicts in treatment. Ir J Psychol Med 13: 62–64
BACKGROUND: Long-term results of minimal intervention strategies to	Oude Voshaar R. C., Gorgels W. J.

cut down benzodiazepine use are not available.OBJECTIVE: To evaluate the relapse rate over a two-year period and to search for predictors of relapse among patients who quit benzodiazepine use after receiving a discontinuation letter.METHODS: Baseline assessment and prospective monitoring of the medical records of 109 patients who quit long-term benzodiazepine use after a minimal intervention strategy in general practice.RESULTS: After 819 +/- 100 days of follow-up, 53 (49%) patients had remained completely abstinent. Two independent predictors of relapse were identified by Cox regression analysis: use of more than 10 mg diazepam equivalent (RR = 2.4 [1.2 - 4.7]) and poor general health perception (RR = 0.98 [0.97 - 0.99]).CONCLUSION: Short-term success rates after a minimal intervention were maintained well during long-term follow-up. High-dose users have the highest risk of relapse.	M. J., Mol A. J. J., Van Balkom A. J. L. M., Van de Lisdonk E. H., Breteler M. H. M. et al. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-conditioned, randomised controlled trial. Br J Psychiatry 2003; 182 : 498–504 **RCT**
OBJECTIVE: To identify predictors of resumed benzodiazepine use after participation in a benzodiazepine discontinuation trial.METHOD: We performed multiple Cox regression analyses to predict the long-term outcome of a 3-condition, randomized, controlled benzodiazepine discontinuation trial in general practice.RESULTS: Of 180 patients, we completed follow-up for 170 (94%). Of these, 50 (29%) achieved long-term success, defined as no use of benzodiazepines during follow-up. Independent predictors of success were as follows: offering a taper-off program with group therapy (hazard ratio [HR] 2.4; 95% confidence interval [CI], 1.5 to 3.9) or without group therapy (HR 2.9; 95% CI, 1.8 to 4.8); a lower daily benzodiazepine dosage at the start of tapering off (HR 1.5; 95% CI, 1.2 to 1.9); a substantial dosage reduction by patients themselves just before the start of tapering off (HR 2.1; 95% CI, 1.4 to 3.3); less severe benzodiazepine dependence, as measured by the Benzodiazepine Dependence Self-Report Questionnaire Lack of Compliance subscale (HR 2.4; 95%CI, 1.1 to 5.2); and no use of alcohol (HR 1.7; 95% CI, 1.2 to 2.5). Patients who used over 10 mg of diazepam equivalent, who had a score of 3 or more on the Lack of Compliance subscale, or who drank more than 2 units of alcohol daily failed to achieve long-term abstinence.CONCLUSIONS: Benzodiazepine dependence severity affects long-term taper outcome independent of treatment modality, benzodiazepine dosage, psychopathology, and personality characteristics. An identifiable subgroup needs referral to specialized care.	Oude Voshaar R, Gorgels W, Mol A, et al. (2006b) Long-term outcome of two forms of randomised benzodiazepine discontinuation. Br J Psy-chiatry 188: 188–189. **RCT**
Background: Discontinuation of benzodiazepine usage has never been evaluated in economic terms. This study aimed to compare the relative costs and outcomes of tapering off long-term benzodiazepine use combined with group cognitive behavioural therapy (TO+CBT), tapering off alone (TOA) and usual care. **Method**: A randomised controlled trial was conducted, incorporating a costeffectiveness analysis from a societal as well as a pharmaceutical perspective. The cost of intervention treatment, prescribed drugs, healthcare services, productivity loss, and patients' costs were measured using drug prescription data and cost diaries. Costs were indexed at 2001 prices. The principal outcome was the proportion of patients able to discontinue benzodiazepine use during the 18- month follow-up. A secondary outcome measure was quality of life (Health Utility Index Mark III [HUI-3] and the Medical Outcomes Study 36-item ShortForm Health Survey [SF-36]).**Results**: A total of 180 patients were randomised to one of TO+CBT (n = 73),TOA (n = 73) or usual care (n = 34). Intervention treatment costs were an averageof €172.99 per patient for TO+CBT and €69.50 per patient for TOA. Both treatment conditions significantly reduced benzodiazepine costs during follow-up compared with usual care. The incremental cost-effectiveness ratios (ICERs) showed that, for each incremental 1% successful benzodiazepine discontinuation,TO+CBT cost €10.30–62.53 versus usual care, depending on the study perspective.However, TO+CBT was extendedly dominated or was dominated by TOA.This resulted in ICERs of €0.57, €10.21 and €48.92 for TOA versus usual care from the limited	Oude Voshaar R. C., Krabbe P. F. M., Gorgels W. J. M. J., Adang E. M. M., van Balkom A. J. L. M., van de Lisdonk E. H. et al. Tapering off benzodiazepines in long-term users: an economic evaluation. Pharmacoeconomics 2006; 24: 683– 94. **economic evaluation** **RCT**

pharmaceutical, comprehensive pharmaceutical and societal perspective, respectively. **Conclusions:** TO+CBT and TOA both led to a reduction in benzodiazepine costs. However, it remains uncertain which healthcare utilisation has a causal relationship with long-term benzodiazepine consumption or its treatment. Although the ICERs indicated better cost effectiveness for TOA than for TO+CBT, the differences were relatively small. The addition of group CBT to tapering off had no clinical or economic advantages. Extrapolation of our data showed that the investment in TOA was paid back after 19 months when corrected for treatmentgain with usual care.	