Rapport

Helsedirektoratet

What is the knowledge base for tapering from OMT-medications (methadone or buprenorphine)

Report IV – Consensus Conference OMT and pregnancy

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FORORD

The Norwegian Directorate of Health has commissoned in all 6 different reviews/reports to be made for the «Norwegian Consensus Conference on Opioid Maintenance Treatment in Pregnancy", which is being organised in Oslo 13.-14. June 2017.

This report is the fourth in the series and will be presented by the author on June 14. 2017 at Holmenkollen Park Hotel.

INNHOLD

INNHOLD

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Hva er kunnskapsbasen for avvenning fra OMT-medikamenter (metadon eller buprenorfin)?

I. Basal neurobiologi

Avvenning fra OMT bør baseres på etablerte metoder i behandling av opioid avhengighet. Konklusjonen er grunnet på generell litteratur om opioid avhengighet.

II. Generell kunnskap om avvenning

Konklusjonen er samlet sett at gradvis nedtrapping med et opioid gir bedre resultater enn avvenning ved behandling med α-adrenerge medikamenter. Metadon og spesielt buprenorfin bør være førstevalg. Avvenning i institusjon er tryggere men poliklinisk behandling kan være et riktig valg for noen, særlig i tidlige faser av avvenningen. Avvenning under anestesi eller dyp sedasjon har ikke støtte. OMT bør ikke planlegges med obligatorisk tidsavgrensning. All behandling av abstinenssymptomer bør skje innen en ramme med planlagt oppfølging og videre behandling. Skjermet situasjon er oftest nødvendig ved alvorlig avhengighet, men poliklinisk avvenning kan være vellykket for motiverte pasienter. Anbefalingene er basert på metastudier hentet fra Cochrane og andre databaser for systematiske revjuer og kan vurderes som grade A kunnskap.

III Kunnskap om avvenning fra OMT behandling

Søket identifiserte 1018 reviews og 4230 primære studier. 53 ble valgt til kunnskapsinnhentingen. I tillegg ble 12 studier hentet fra referanselistene til de valgte studiene. De RCT'ene som ble funnet er for det meste små og har i stor grad ulikheter i metodikk og er dessuten bare relevante for enkelte av de spørsmålene som er vurdert. Kunnskapen er derfor på nivå c-d bedømt ved grading.

III-1 Avvenningen

Andel med fullført nedtrapping varier fra 0 % – 100 %, typisk sett fra 10 % - 70 % når man utelukker studier av avvenning i narkose og nedtrapping i OMT-programmer som er innstilt på

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livslang behandling og ikke støtter nedtrapping. Det er ikke mulig å fastslå noe bestemt nivå men man kan anslå at avvenningen ofte er mulig for ca 20 % av hele OMT-populasjonen.
Oppfølgingsperioden i studiene varierer fra dager til flere år.
Tilbakefall til bruk av illegale opioider er vanlig, særlig første måned. Etter tre år blir tilbakefallene sjeldnere men forkommer. 5-15 % finnes typisk sett med vedvarende stoffrihet.
Gjeninntak bør være lett tilgjengelig
Mortalitet, morbiditet, kriminalitet og andre uønskete hendelser. Problemene er sterkt økte de første 1-3 månedene og stabiliseres deretter typisk sett på nivået før OMT. Den økte morbiditeten er særlig knyttet til injeksjonsbruk.
Brukertilfredshet og livskvalitet øker ved oppnådd og særlig ved vedvarende stoffrihet.

III-2. Særlige elementer i avvenningen
Grunner til og motivasjon for avvenning: Vanlige grunner er motvilje mot kontrolltiltak, opplevelse av at pårørende og andre ønsker det, ønske om yrkesmessig og/eller sosial rehabilitering. Når motivasjonen er knyttet til negative reaksjoner på behandlingsopplegget, tenderer resultatene til å bli svakere. Disiplinære holdninger i staben kan være assosiert med svakere resultater.
Frivillig mot ufrivilling avvenning: Tendensen i studiene er at disiplinære utskrivninger er assosiert med høyere nivå av mortalitet og svakere psykososiale tilpasning. Funnet kan ha sammenheng med dårligere prognose hos de som av ulike grunner har utilstrekkelig nytte av OMT.
Hvor viktig er stoffriht og sosial rehabiliteirng (recovery)? "Recovery" – langvarig "stoffrihet" er assosiert med større tilfredshet og bedre angitt livskvalitet. Seleksjon av et positivt utvalg kan være en delforklaring.
Kan det vises ulike problemer og vansker knyttet til valg av OMT-agonist? Forskjellene er ikke markerte men buprenorfin er assosiert med noe mindre abstinensvansker og metadon med noe høyere mortalitetsrisiko.
Anbefalinger for særlige avvenningsregimer og prosedyrer: Det kan være nyttig å trappe ned doseringen av agonist gradvis, eventuelt med stabiliseringsperioder. For MMT kan det være nyttig å redusere til ca 30 mg metadon og deretter skifte til buprenorfin og bruke dette gjennom resten av nedtrappingen. Det er flere rapporter om nytte av skjerming, særlig i avsluttende

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faser. Tilbakefallsforebygging med langvarige virkende antagonister (slow release naltrexon preparations) kan bedre forløpet.

III-3 Prognostiske faktorer er knyttet til pasientens resurser og til seleksjon av og situasjon for pasienter som ønsker nedtrapping. Angstreaksjoner (nedtrappingsangst og fobi) og affektive reaksjoner, særlig depressive tilstander – en sjelden gang psykoser, kan hindre og vanskeliggjøre nedtrappingen.

III-4 Videre forskning: Det er ønskelig med longitudinelle kohortstudier med bruk av koplete kvantitative og kvalitative metoder. Nasjonale register studier med nærstudier av strategiske kasusutvalg av pasienter som avslutter OMT. Det er ønskelig med systematisk undersøkelse av verdien av antagonister med langvarig virkning og studier av grad av nevroplastiske endringer, gjerne sammen med analyser av genetisk basert vulnerabilitet og resiliens.

LAR legemiddelassistert rehabilitering
DOR ɗ-opioidreseptor
MOR µ-opioidreseptor
KOR ƙ -opioidreseptor
GD fosterdag (gestation day)
PND dag etter fødsel (postnatal day)

SUMMARY - ENGLISH

What is the knowledge base for tapering for OMT-medications (methadon or buprenorphine)

I. Basic neurobiology

Tapering from OMT drugs should be based on methods known in treatment of opioid dependency. The conclusion is inferred from general literature on opioid dependency.

II. General knowledge on detoxification

The overriding conclusion is that opioid tapering is superior to detoxification with α-adrenergic drugs. Methadone and especially buprenorphine are to be preferred. Inpatient setting is safer but out-patient approach is relevant for some. Detoxification during aesthesia or deep sedation is not supported. OMT should not have any time limitation. Treatment of opioid withdrawal symptoms should be followed by referral. Supported setting is necessary for severely dependent addicts, but outpatient tapering might be successful for motivated patients.
The conclusion is based on systematic reviews as found in Cochrane and other databases of systemtic reviews and should be graded on level A.

III Research on OMT tapering

The search identified 1018 reviews and 4230 primary studies. 53 were selected for the review. Additional 12 studies were identified by studying reference lists in selected studies. The knowledge base is by grading found on level c-d. The identified RCT studies are small and characterized by differences in client selection and research methods. Those found are only relevant for some of the questions investigated.

III-1 . General findings on OMT tapering

Treatment completion varies from 0 % – 100 %, typically from 10 % - 70 % excluding tapering supported by anaesthesia and tapering in programs encouraging indefinite treatment. It is not possible to infer any general valid level but findings indicate that completed tapering is often possible for about 20 % of total OMT populations.
Follow up period varies from days to several years.

SUMMARY - ENGLISH

Relapse to use of illegal opioids is frequent, particularly first month. Relapse after three years are relatively seldom but do occur. Enduring abstinence is typically found in the range of 5-15 %.
Re-intake in OMT should be easily available
Mortality, criminal activity, morbidity and other unwanted events. Mortality and criminality is increased the first 1-3 months. Morbidity is particularly linked to relapse of injecting drug taking.
User satisfaction increases after successful and sustained abstinence.

III-2. Specific elements
Reasons and motivations for tapering . Clients are often motivated by resentment of control, perceived needs among significant others, wish for vocational and social rehabilitation. Motivation linked to perceived negative aspects of treatment tends to be associated with poor outcome. Disciplinary attitudes among staff are associated with poor results.
Voluntary versus involuntary tapering Disciplinary tapering is linked to high mortality and high level of relapse.
Importance of drug free states and social rehabilitation (recovery) Recovery is associated with higher satisfaction and life quality but selection factors might be involved.
Differential problems and/or results according to type of agonist involved? Buprenorphine is associated with less severe withdrawal symptoms. Methadone is associated with a higher risk of mortality.
Recommendations for specific tapering regimes and procedures. It might be useful to reduce treatment dosage gradually with stabilizing periods. Cross-over to buprenorphine at 20 – 30 mg is found useful in methadone taper. Protected environment might be necessary. Sustained release antagonist treatment post taper might improve results

III-3 Prognostic factors are linked to resources and selection. Anxiety reaction (fear and phobia), depressive reactions and more seldom psychosis, might hinder and complicate tapering.

III-4 Future research: Cohort studies of clients leaving OMT with coupled qualitative and quantitative methods. National register studies of patients leaving OMT. Trials with slow release antagonists. Neurobiological studies on level of neuroplastic changes, preferably strengthened by analyses of genetic vulnerability and resilience.

1. BASIC NEUROBIOLOGY

The biological aspects of opioid dependency are linked to neuroplastic changes involving neuroadaptation in cells with opioid receptors and changes that have developed in their neuronal connections.

- Are there any indications that opioids used in OMT cause different or stronger abstinence problems than opioids with shorter half-life more often used as intoxicants such as heroin?

- Are there any evidence that detoxification from OMT should necessitate differential approaches or methodology compared to detoxification from dependency cause by use of heroin?

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These questions are answered on basis of general knowledge as stated in textbooks and core papers in well-known journals with neurobiological orientation without literature search.

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All opioids bind to specialized opioid receptors. Those acting as agonists stimulate the receptor. This induces a range of changes in neuronal activity with consequences depending on the location in the nervous system. There are three types of opioid receptors; μ, δ, κ with differential functions. μ is the core receptor for opioid dependency particularly through high density on GABA-neurons in VTA and Subst. Nigra. Their effect is to inhibit the inhibitory GABA-neurons with a consequential increase of dopamine release in nucleus accumbens and related areas. The neuroplasticity involved cause changes in the reward patterns that increase liking and wanting of continued opioid use and a tendency to anhedonic states and craving for opioids during and after tapering. In addition the opioids have a depressive effect on several brain centers and areas, among them in particular locus coerulus. This center has a regulatory effect on the brain cortex and the sympathetic nerve system in particular. Depressive effects reduce general cerebral activity and low level of noradrenergic transmissions. Tapering tend to cause general agitation with anxiety and depressive reaction while increased noradrenergic activity have consequences for hart rate, blood pressure, bowel functions, sweat glands and dimensions in skin blood circulation. As often seen, the reality is more complex as new findings elucidate different aspects of the phenomena. Recent research has emphasized that opioide influence causes important changes in protein production in the cells involved (Stockton et al

2014). These have relevance for the development of neuronal network and the functions in the frontal cortex, hippocampus and other structures important for cognitive processes. Further, there has been increasing focus not only on types and subtypes of receptors but also on efficacy, intrinsic activity and intrinsic efficacy. It is not only the affinity, the ability to bind to the receptors that determines the properties of the agonist but also the ability to activate the receptors and to produce cellular response. There might also be possible to differentiate effects on different brain functions as for instance analgesic effect and the effect on modulating the receptor structure and intracellular responses – neuroadaptation and development of tolerance. So far there has been no breakthrough, but the possibility remains. In addition the efficacy might also be context dependent so that the same agonist might be more efficient in one context than in another (Kelly 2013). Finally the genetics of opioid receptors might be even another complicating field of research. Studies indicate that polymorphisms influence the type and reactivity of receptors and the severity and duration of withdrawal (Jones et al 2016). The findings are important for the understanding of dependence and addiction, but so far there is no evidence for differential effects of different opioids beyond differences connected to full- and partial agonists, primarily a question of strength of receptor activation.

All these effects are linked to the stimulation of the opioid receptors per se. One has found a high number of subtypes of for instance the μ-receptor. It has been speculated that differential effects of different opioids might explain some variations in for instance analgesic effects, but so far there is no indications that opioids with short term effects used as intoxicants and those with sustained effects used as maintenance agonists are caused by different receptor functions. The differential effects are linked to rapidity of penetration of the drug from intake to stimulation of receptor, the characteristics of the binding to receptor and the metabolism of the drug. Heroin and other attractive drugs have more intensive drug effects that last relatively short and given neuroadaptation, consequently also to more intensive drug wanting and abstinence reactions. The drug euphoria and drug wanting connected to long acting maintenance drugs are correspondingly weaker than that of short acting drugs but tend to last longer. It can be argued that maintenance treatment involves a more constant and regular use of an opioid at a higher dosage than ordinarily available in illegal use of heroin. This might cause stronger problems in tapering, but this has never been demonstrated in clinical research. There are reports from individuals complaining of dramatic problems in OMT tapering, but the typical observation is moderate problems in tapering until a low level such as 20-30 mg methadone and 2-4 mg buprenorphine.

The different opioids do have other effects related to of their differential molecules. Methadone is a full agonist stimulating all types of opioid receptors in the same way as heroin, but in addition one has found inhibitory effects on the stimulating NMDA receptors. This might cause an extra tendency to inhibitory or depressive effects on some brain functions and regulatory systems with corresponding stimulation when the drug effect is diminishing. It is however, difficult to understand why the relatively weak NMDA effects should cause particular problems in tapering. Buprenorphine

is a partial agonist and seems not to influence the κ-receptors. Further, it has limited dose effect relationship as dose increase beyond 24-32 mg buprenorphine do not seem to increase the stimulation of the receptor. One would accordingly expect a maximum level of neuroadaptation. This might indicate lower level of problems in tapering.

1.1 The conclusion

would be that there is no neurobiological basis for any claim that tapering from OMT drugs necessitates other approaches than those used in tapering and detoxification in treatment of heroin dependency. There might however be different levels of withdrawal in full and partial agonist dependencies.

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2. GENERAL KNOWLEDGE ON DETOXIFICATION IN OPIOID DEPENDENCY

Treatment of withdrawal symptoms and approaches in detoxification related to opioid dependency

What are the present recommendations according to well-known reviews and meta-studies?

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These questions are answered on basis of Cochrane reviews, WHO, BAP and Nice recommendations and the Norwegian guideline.

Tapering and detoxification involves reduction of the opioid stimulation of opioid receptors. Stimulation causes neuroadaptation and neuroplasticity changes in the receptors systems, and this implies downgrading of several neuronal functions. The typical consequence is symptoms opposite to those induced by the opioids. There are three typical reactions: Activation of the sympathetic nerve systems – high level activity in noradrenergic nerves. Increase in general brain activity often experienced as anxiety and panic – alarm reactions. Feelings of anhedonia and drug wanting influencing motivational processes. The first type is often the most obvious "abstinence symptoms" and lasts usually the first to the third week. The others have duration of months. In addition: Reversal of neuroadaptation will decrease and reverse the tolerance for the drugs rendering the user vulnerable for overdose mortality.

While low level dependency might be met with "cold turkey" – psychosocial support and psychological interventions only, dependency of the degree involved in addictive disorders usually cause abstinence reactions necessitating biological treatment. Three approaches can be recognized: 1. use of specific drugs directed at gastrointestinal symptoms, muscular pains and general anxiety and sleep problems, 2. drugs specifically aimed at hyper adrenergic states and 3. opioids used in decreasing doses (tapering). The first type might be used according to need while the others are specific detoxification technologies.

There are several reviews comparing the different approaches. The overriding conclusion is that use of α-adrenalin agonists or opioid tapering reduces problematic symptoms more effectively than psychosocial support alone, but also that the psychosocial support increases the success rate of psychopharmacological approaches (Amato et al 2011). Prevalence of drop out is lower and the percentage that fulfil the detoxification process higher. Use of specific detoxification technologies is therefore recommended, preferably combined with psychosocial support and problem-solving. Use of α-adrenalin agonists reduces symptoms of adrenergic hyperactivity on level with opioid tapering, but craving for opioids is less reduced (Gowing et al 2014). Opioid tapering is therefore superior to detoxification based on α-adrenergic drugs (Meader 2010). The latter should therefore be reserved for moderate dependency patients and situations where use of opioid drugs for some reason is difficult. It might also be an important approach when the patient plans for antagonist treatment for instance with naltrexone depot injections.

The basic approach in tapering and detoxification is to induce a slowly diminishing stimulation of the opioid receptor. This allows for normalization and all the different opioid agonists might be used. The drug of choice was earlier morphine either as injections or as tablets. Presently meta-studies indicate that methadone (Amato et al 2011) and especially buprenorphine (Gowing et al 2009) are safer in use and to be preferred by the possibility of less frequent administration. WHO (2009) recommends methadone, mainly on basis of costs, but no studies have demonstrated differential level of side effects or higher success rates comparing methadone with buprenorphine (Meader 2010). Gowing et al (2009) do however find a slight increase in goal attainment (to reach opioide abstinence) with use of buprenorphine and a repeat study (Gowing et al 2017) finds indications that withdrawal symptoms might resolve more quickly. For out-patient detoxification buprenorphine, and in particular buprenorphine-naloxone combinations, is recommended on safety basis (Dunn et al 2011). Some other opioid agonist such as slow release morphine (SROM), opium and codein have also been investigated but none has been recommended (Madlung-Kratzer et al 2009, Nikoo et al 2017). Detoxification during aesthesia or deep sedation has been used to avoid drop-out and high levels of discomfort. According to a Cochrane review antagonist-induced withdrawal under heavy sedation or anaesthesia is not supported in view of risks, costs and moderate level benefits compared to other approaches (Gowing et al 2010). It is possible to introduce antagonists to speed up detoxification with minimal sedation for instance with use of opioid antagonists combined with alpha$_2$-adrenergic agonists. However, it is unclear whether this approach reduces the duration of withdrawal or facilitates transfer to naltrexone treatment to a greater extent than withdrawal managed primarily with an adrenergic agonist.

Two other aspects are of relevance. Firstly; what are the indications and contraindications for detoxification and tapering. The other is recommendations on duration of and setting for tapering. While OMT initially was seen as time limited treatment, a vast number of follow up studies have found involuntary detoxification to be followed by increased mortality and morbidity. The overriding recommendation is presently that OMT should not have any time limitation but be continued unless the patient actively wants to end OMT. Also for patients dependent on illegal opioids or under opioid treatment for medical conditions, tapering and detoxification lead to periods of increased overdose mortality and decreased ability to comply with medical interventions and with the demands of self

care. However, when seen as a gateway to indicated and individually tailored long term treatment, detoxification might be indicated ant the approach chosen selected accordingly (Gowing & Ali 2006). The conclusions reached in guidelines (Lingford-Hughes et al 2011, Helsedirektorat 2016, Nice) is largely identical. Opioid detoxification should not be routinely offered to people except when there is a medical condition needing urgent treatment, in police custody, serving a short prison sentence or a short period of remand. In emergency settings primary problem should be addressed and the opioid withdrawal symptoms treated with referral to further drug services as appropriate. Consideration should always be given to treat opioid withdrawal symptoms with opioid agonist medication in a perspective of continuity in treatment.

As to duration, the literature has mainly recommendations based on open uncontrolled studies. The usual clinical recommendation is that duration should be guided by patient development and by clinical observations. This means that the tapering might be guided by the seriousness of withdrawal symptoms, preferably measured by symptom scales such as OWS. While some might resolve their problems faster, the typical duration is seen in relation to the adrenergic period of one to three weeks followed by a protracted period that have high tendency to relapse. One systematic review investigated the duration of outpatient buprenorfin detoxification (Dunn et al 2011). The finding was that while the level of opiate abstinence during tapering was influenced by the duration, the retention rate or level of success (reaching stable opiate abstinence) was not. The decisive factors seem to be degree of dependence, personal resources and type of continued treatment and support.

As to setting, the usual recommendation for severely dependent addicts is tapering in closed or at least supported settings in view of increased mortality, particularly when tapering with methadone. Tapering might be initiated in outpatients, but as withdrawal symptoms increase, both risk of drop out and overdose incidents become dangers and obstacles. However, there are several reports that outpatient tapering with buprenorphine or buprenorphine-naloxone might be successful for patients motivated for opiate abstinence. The relapse rates are however, high, particularly in patients with moderate or severe degree of dependency unless taper is followed by slow release naltrexone and community support systems.

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3. SPECIFIC KNOWLEDGE ON "EXIT OMT" – APPROACHES AND RESULTS IN DETOXIFICATION IN OMT PROGRAMS

The questions to be answered are the following:

1. What is the knowledge base about tapering of OMT-drugs (review papers, RCT-studies, cohort studies with and without control- or comparison groups.)

- Treatment completion (full tapering of agonist drug**)**
- Follow up period
- Relapse to use of illegal opioids (abstinence rates)
- Re-intake in OMT
- Mortality, criminal activity, morbidity and other unwanted events. r
- User satisfaction and changes in psychosocial functioning

2. Do any specific elements/factors influence termination of OMT and tapering of OMT drugs?

- Reasons and motivations for tapering – or not tapering
- Consequence of type of termination of OMT / Voluntary versus involuntary tapering
- Importance of drug free states and social rehabilitation (recovery)
- Differential problems and/or results according to type of agonist involved?
- Recommendations for specific tapering regimes and procedures (duration, user influence)

3. Prognostic factors influencing success in tapering and prevalence of relapse to use of heroin.

4. Future research

4. LITERATURE SURVEY

These questions were investigated by a separate literature survey performed by Norwegian Institute of Public Health combined with surveys performed planning OMT in Norway and investigating strategies for “Exit LAR”. The search was performed by Marita Heintz, Department of Library Services in the Norwegian Institute of Public Health. The aim was to find papers with

a) Systematic or casuistic evaluations of withdrawal problems met by tapering of patients treated in OMT. Comparison between different agonist drugs is important (methadone, buprenorphine, morphine, heroin, codeine). Differences between detoxification in OMT and opioid dependency without OMT in approaches, symptomatology, duration og severity.

b) Descriptions and evaluations of tapering and detoxification from OMT (theoretical, methodological and contextual approaches)

c) Follow-up studies and cohort studies, preferably with descriptions of selections and goal attainment, if possible related to type of OMT agonist.

d) RCT and other types of controlled studies if possible; meta-studies.

Search strategy was based on subject headings and text words in titles and abstract. Table 1 gives an overview.

Table 1. Research strategy and findings.

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date: 06.02.2017

Found**:** 2310 (270 reviews, 2040 primær)

1	Opiate Substitution Treatment/ or buprenorphine/ or Buprenorphine, Naloxone Drug Combination/ or methadone/	15070
2	Withholding Treatment/ or Substance Withdrawal Syndrome/	30272
3	1 and 2	1387
4	(((maintenance or replacement or substitution) adj1 (treatment? or therap*) adj5 (withdraw* or detoxification? or abstinence or termination? or terminate or quit or quits or "dose reduction?" or discontinu* or "time limited" or timelimited or taper* or exit?)) and (opioid or opiate)).tw.	120
5	((buprenorphin* or buprenorfin* or Buprenex or Prefin? or Subutex or Temgesic or Buprex or "6029 M" or 6029M or RX6029M or anorfin? or belbuca or buprin? or butrans or "cl 112 302" or "cl 112302" or "cl112 302" or cl112302 or finibron? or lepetan or "nih 8805" or nih8805 or norphin? or norfin? or pentorel or transtec or "um 952" or um952 or methadon* or Biodon? or Dolophin? or Metadol or Symoron or Methadose or Methex or Phenadon? or Physepton? or Phymetor or Phymet or Amidon? or Methaddict or adanon or algidon? or algolysin? or algoxale or althose or amidosan? or "an 148" or an148 or anadon or butalgin? or deamin? or depridol? or diaminon? or dianon? or dolafin? or dolamid or doleson? or dolmed or dorex or dorexol? or eptadon? or fenadon? or gobbidon? or heptadon? or heptanon? or "hoe 10820" or hoe10820 or ketalgin or mecodin or mepecton? or mephenon? or metadon* or metasedin? or methaforte mix or miadon? or moheptan or pallidon? or polamidon? or polamivet or polamivit or sinalgin or westadon? or "bunavail" or "suboxone" or "zubsolv" or naloxonebuprenor* or methenex) adj5 (withdraw* or detoxification? or abstinence or termination? or terminate or quit or quits or "dose reduction?" or discontinu* or "time limited" or timelimited or taper* or exit?)).tw.	1343
6	3 or 4 or 5	2310
7	limit 6 to "reviews (best balance of sensitivity and specificity)"	270
8	6 not 7	2040

Database: Embase 1974 to 2017 February 03

Dato: 06.02.2017

Antall treff: 4334 (857 reviews, 3477 primær)

1	opiate substitution treatment/ or buprenorphine/ or buprenorphine plus naloxone/ or methadone/ or methadone plus naloxone/ or methadone treatment/
2	treatment withdrawal/ or withdrawal syndrome/
3	1 and 2
4	(((maintenance or replacement or substitution) adj1 (treatment? or therap*) adj5 (withdraw* or detoxification? or abstinence or termination? or terminate or quit or quits or "dose reduction?" or discontinu* or "time limited" or timelimited or taper* or exit?)) and (opioid or opiate)).tw.
5	((buprenorphin* or buprenorfin* or Buprenex or Prefin? or Subutex or Temgesic or Buprex or "6029 M" or 6029M or RX6029M or anorfin? or belbuca or buprin? or butrans or "cl 112 302" or "cl 112302" or "cl112 302" or cl112302 or finibron? or lepetan or "nih 8805" or nih8805 or norphin? or norfin? or pentorel or transtec or "um 952" or um952 or methadon* or Biodon? or Dolophin? or Metadol or Symoron or Methadose or Methex or Phenadon? or Physepton? or Phymetor or Phymet or Amidon? or Methaddict or adanon or algidon? or algolysin? or algoxale or althose or amidosan? or "an 148" or an148 or anadon or butalgin? or deamin? or depridol? or diaminon? or dianon? or dolafin? or dolamid or doleson? or dolmed or dorex or dorexol? or eptadon? or fenadon? or gobbidon? or heptadon? or heptanon? or "hoe 10820" or hoe10820 or ketalgin or mecodin or mepecton? or mephenon? or metadon* or metasedin? or methaforte mix or miadon? or moheptan or pallidon? or polamidon? or polamivet or polamivit or sinalgin or westadon? or "bunavail" or "suboxone" or "zubsolv" or naloxonebuprenor* or methenex) adj5 (withdraw* or detoxification? or abstinence or termination? or terminate or quit or quits or "dose reduction?" or discontinu* or "time limited" or timelimited or taper* or exit?)).tw.
6	3 or 4 or 5
7	Elsevier.cr.
8	6 and 7
9	limit 8 to "reviews (best balance of sensitivity and specificity)"
10	8 not 9

Database: Web of Science

Dato: 06.02.2017

Antall treff: 1066 (95 reviews, 971 primær)

# 4	**95**	#2 OR #1) *AND* **DOCUMENT TYPES:** (Review) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 3	**1,066**	#2 OR #1 *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 2	**1,016**	**TOPIC:** ((("buprenorphin*" or "buprenorfin*" or "Buprenex" or "Prefin$" or "Subutex" or "Temgesic" or "Buprex" or "6029 M" or "6029M" or "RX6029M" or "anorfin$" or "belbuca" or "buprin$" or "butrans" or "cl 112 302" or "cl 112302" or "cl112 302" or "cl112302" or "finibron$" or "lepetan" or "nih 8805" or "nih8805" or "norphin$" or "norfin$" or "pentorel" or "transtec" or "um 952" or "um952" or "methadon*" or "Biodon$" or "Dolophin$" or "Metadol" or "Symoron" or "Methadose" or "Methex" or "Phenadon$" or "Physepton$" or "Phymetor" or "Phymet" or "Amidon$" or "Methaddict" or "adanon" or "algidon$" or "algolysin$" or "algoxale" or "althose" or "amidosan$" or "an 148" or "an148" or "anadon" or "butalgin$" or "deamin$" or "depridol$" or "diaminon$" or "dianon$" or "dolafin$" or "dolamid" or "doleson$" or "dolmed" or "dorex" or "dorexol$" or "eptadon$" or "fenadon$" or "gobbidon$" or "heptadon$" or "heptanon$" or "hoe 10820" or "hoe10820" or "ketalgin" or "mecodin" or "mepecton$" or "mephenon$" or "metadon*" or "metasedin$" or "methaforte mix" or "miadon$" or "moheptan" or "pallidon$" or "polamidon$" or "polamivet" or "polamivit" or "sinalgin" or "westadon$" or "bunavail" or "suboxone" or "zubsolv" or "naloxonebuprenor*" or "methenex") NEAR/4 ("withdraw*" or "detoxification$" or "abstinence" or "termination$" or "terminate" or "quit" or "quits" or "dose reduction$" or "discontinu*" or "time limited" or "timelimited" or "taper*" or "exit$"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*
# 1	**117**	**TOPIC:** ((((("maintenance" or "replacement" or "substitution") NEAR/0 ("treatment$" or "therap*") NEAR/4 ("withdraw*" or "detoxification$" or "abstinence" or "termination$" or "terminate" or "quit" or "quits" or "dose reduction$" or "discontinu*" or "time limited" or "timelimited" or "taper*" or "exit$")) and ("opioid" or "opiate"))) *Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI Timespan=All years*

Database: Cochrane Database of Systematic Reviews : Issue 2 of 2, February 2017, Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015, Cochrane Central Register of Controlled Trials : Issue 1 of 12, January 2017, Cochrane methodology register : Issue 3 of 4, July 2012, Health Technology Assessment Database : Issue 4 of 4, October 2016, NHS Economic Evaluation Database : Issue 2 of 4, April 2015

Dato: 06.02.2017

Antall treff: 661 (CDSR: 24, DARE: 13, Trials: 612, Method: 1, Tech ass: 4, Eco: 7)

#1	[mh ^"Opiate Substitution Treatment"]	231
#2	[mh ^buprenorphine]	754
#3	[mh ^"Buprenorphine, Naloxone Drug Combination"]	35
#4	[mh ^methadone]	1011
#5	#1 or #2 or #3 or #4	1634
#6	[mh ^"Withholding Treatment"]	279
#7	[mh ^"Substance Withdrawal Syndrome"]	1851
#8	#6 or #7	2124
#9	#5 and #8	233
#10	(((maintenance or replacement or substitution) near/1 (treatment or treatments or therap*) near/5 (withdraw* or detoxification or detoxifications or abstinence or termination or terminations or terminate or quit or quits or "dose reduction" or "dose reductions" or discontinu* or "time limited" or timelimited or taper* or exit or exits)) and (opioid or opiate)):ti,ab,kw	34
#11	(((maintenance or replacement or substitution) near/1 (treatment or treatments or therap*) near/5 (withdraw* or detoxification or detoxifications or abstinence or termination or terminations or terminate or quit or quits or "dose reduction" or "dose reductions" or discontinu* or "time limited" or timelimited or taper* or exit or exits)) and (opioid or opiate)) in Other Reviews, Technology Assessments and Economic Evaluations	4
#12	((buprenorphin* or buprenorfin* or Buprenex or Prefin or Prefin? or Subutex or Temgesic or Buprex or "6029 M" or 6029M or RX6029M or anorfin or anorfin? or	541

	belbuca or buprin or buprin? or butrans or "cl 112 302" or "cl 112302" or "cl112 302" or cl112302 or finibron or finibron? or lepetan or "nih 8805" or nih8805 or norphin or norphin? or norfin or norfin? or pentorel or transtec or "um 952" or um952 or methadon* or Biodon or Biodon? or Dolophin or Dolophin? or Metadol or Symoron or Methadose or Methex or Phenadon or Phenadon? or Physepton or Physepton? or Phymetor or Phymet or Amidon or Amidon? or Methaddict or adanon or algidon or algidon? or algolysin or algolysin? or algoxale or althose or amidosan or amidosan? or "an 148" or an148 or anadon or butalgin or butalgin? or deamin or deamin? or depridol or depridol? or diaminon or diaminon? or dianon or dianon? or dolafin or dolafin? or dolamid or doleson or doleson? or dolmed or dorex or dorexol or dorexol? or eptadon or eptadon? or fenadon or fenadon? or gobbidon or gobbidon? or heptadon or heptadon? or heptanon or heptanon? or "hoe 10820" or hoe10820 or ketalgin or mecodin or mepecton or mepecton? or mephenon or mephenon? or metadon* or metasedin or metasedin? or methaforte mix or miadon or miadon? or moheptan or pallidon or pallidon? or polamidon or polamidon? or polamivet or polamivit or sinalgin or westadon or westadon? or "bunavail" or "suboxone" or "zubsolv" or naloxonebuprenor* or methenex) near/5 (withdraw* or detoxification or detoxifications or abstinence or termination or terminations or terminate or quit or quits or "dose reduction" or "dose reductions" or discontinu* or "time limited" or timelimited or taper* or exit or exits)):ti,ab,kw	
#13	((buprenorphin* or buprenorfin* or Buprenex or Prefin or Prefin? or Subutex or Temgesic or Buprex or "6029 M" or 6029M or RX6029M or anorfin or anorfin? or belbuca or buprin or buprin? or butrans or "cl 112 302" or "cl 112302" or "cl112 302" or cl112302 or finibron or finibron? or lepetan or "nih 8805" or nih8805 or norphin or norphin? or norfin or norfin? or pentorel or transtec or "um 952" or um952 or methadon* or Biodon or Biodon? or Dolophin or Dolophin? or Metadol or Symoron or Methadose or Methex or Phenadon or Phenadon? or Physepton or Physepton? or Phymetor or Phymet or Amidon or Amidon? or Methaddict or adanon or algidon or algidon? or algolysin or algolysin? or algoxale or althose or amidosan or amidosan? or "an 148" or an148 or anadon or butalgin or butalgin? or deamin or deamin? or depridol or depridol? or diaminon or diaminon? or dianon or dianon? or dolafin or dolafin? or dolamid or doleson or doleson? or dolmed or dorex or dorexol or dorexol? or eptadon or eptadon? or fenadon or fenadon? or gobbidon or gobbidon? or heptadon or heptadon? or heptanon or heptanon? or "hoe 10820" or hoe10820 or ketalgin or mecodin or mepecton or mepecton? or mephenon or mephenon? or metadon* or metasedin or metasedin? or methaforte mix or miadon or miadon? or moheptan or pallidon or pallidon? or polamidon or polamidon? or polamivet or polamivit or sinalgin or westadon or westadon? or "bunavail" or "suboxone" or "zubsolv" or naloxonebuprenor* or methenex) near/5 (withdraw* or detoxification or detoxifications or abstinence or termination or terminations or terminate or quit or quits or "dose reduction" or "dose reductions" or discontinu* or "time limited" or	23

	timelimited or taper* or exit or exits)) in Other Reviews, Technology Assessments and Economic Evaluations	
#14	or #9-#13	661

We searched Medline, Embase, Cochrane library of systmatic reviews, Database of Abstracts of Reviews of Effect, Cochrane Central Register of Controlled Trials, Cochrane methodology register, Health Technology Assessment Database, NHS Economic Evaluation Database and Web of Science. The search was designed without time limitation with separate searches for review and primary papers. This search identified 1018 reviews and 4230 primary studies after control for duplicates.

The author has adapted this review for the knowledge study. First the references were imported in Endnote. Then papers focusing pain treatment, pregnancy and addiction or other subjects not directly related to substitution treatment were eliminated based on titles and subject. This left 126 papers. Then papers and reviews on maintenance treatment and papers describing or evaluating OMT as such were eliminated by abstracts. This left 53 papers used in the review. Of these seven were theoretical or descriptive papers that dealt with different aspects of OMT versus detoxification, the need and possible indications, speculations on approaches and so. 13 paper focused client characteristics that might cause difficulties in detoxification, one also staff characteristics. There were 16 single studies describing detoxification cohorts with different follow-up periods. Two were register studies analyzing patterns following detoxification form OMT. Eight were RCT projects comparing different approaches in detoxification, detoxification versus continued OMT, differential choice of tapering drugs, different dose choices. None were comparable in aim and detoxification techniques. There were no metastudies but seven systematic reviews. One was included in spite of focus on tapering from dependency caused by pain treatment of non-terminal pain. Another 12 papers were included from reference lists in included papers.

Of the selected papers, 36 were written before 2005. Three reviews summed and evaluated single studies on detox and tapering from OMTY and RCT-studies comparing different approaches in this period (Kornor & Waal, 2005; Magura & Rosenblum, 2001; Milby, 1988).These reviews are used to evaluate findings of studies earlier then 2004. Other studies are read in full when relevant.

The theoretical papers are used in a general introduction to the subject of taper. The first question is whether detoxification at all is indicated. In the early years of OMT, indefinite OMT was controversial (Cushman, 1976; Kleber, 1977; Kremen & Bayer, 1973; Lowinson et al., 1976). Other models such as time limited OMT, interim OMT and dose reduction OMT were alternatives. However, studies comparing continued OMT to enriched 180 days detoxification found the latter

associated with higher levels of relapse to heroin use (Sees et al., 2000) at higher costs (Masson et al., 2004). Methadone reduction programs typically found reduction strategy associated with inferior results (Gossop et al, 2001). Studies of time limited buprenorphine maintenance gave similar results (Kornor et al 2007). Thus the interest in time limitations has diminished. Even so the possibility to routinely taper from OMT was explored until and during the first decade this century. The later studies have mostly focused degree of narcotic abstinence and other aspects of follow up.

4.1 What is the knowledge base about tapering of OMT-drugs (review papers, RCT-studies, cohort studies with and without control- or comparison groups.)

4.1.1 Treatment completion (full tapering of agonist drug)

The early reviews gave differing results. Milby (1988) noted increasing average rates for completion of detoxification increasing from 39.7 % in 1970 -1975 to an average of 76.3 % in the five year period 1980-85. "Therapeutic" detoxifications recommended in programs had clearly increased success-rates compared to not recommended. The increasing success rates were attributed to use of new drugs alieving the withdrawal symptoms. However, no influence on the development in drug use in the follow-up period was detected. The interpretation of the studies is hampered by unclear selections for the detoxification group and widely differing approaches in evaluation. The high percentages groups are found by percentage of groups selected for detoxification, not from the whole OMT in for instance Cushman (Cushman, 1978). Magura & Rosenblum (2001) did not focus completion of detoxification directly but strongly warned against time limitation in view of problematic results in follow-up periods. Kornor & Waal (2005) found 12 studies, mostly naturalistic follow-up of MMT patients. The focus was on maintaining, not on reaching abstinence.

Studies on detoxification assisted by narcosis give extraordinary high percentage detoxification completion compered to studies on detoxification within programs encouraging indefinite OMT. A single study of the latter found that of 30 patients initiating detoxification, none completed methadone tapering. Four patients switched to buprenorphine and one of these completed (Calsyn et al., 2006). Several papers describe involuntary detoxifications marked by poor success (Bentzley et al 2015; Kornor & Waal, 2005; Magura & Rosenblum, 2001). Other papers deal with patient initiated detoxifications. Noble et al (2002) noted that 58 % of 114 patients in a MMT clinic in South London had an average of 3.6 attempts at self-detoxifications with varying motivations (Noble et al 2002). Short term abstinence was reached by 41 %. Gryczinski found that clients in treatment had several reasons for wanting to exit OMT, among them conflicts with staff, involuntary discharge and program inflexibility. 41 % left within 6 months (Gryczynski et al., 2014). A complementary perspective is found in an impressively large study of dose reduction in patients in long term opioid pain therapy

(Frank et al., 2016). The study identified 46 studies with data on 8191 patients. Across studies opioid discontinuation rates ranged from 14 – 100 %.

Single studies with follow-up design are mostly small with few subjects. Population based studies and case file studies might reach larger populations, but the information might be insufficient. One Canadian study stands out (Nosyk et al., 2012). The study was based on linked administrative medication dispensing data. Of 25545 completed MMT episodes, 14602 initiated taper. 4183 individuals with 4917 MMT episodes in the study period met inclusion criteria of taper defined as </= 5 mg/day in the last 4 weeks, 19 % of all. Complete fulfilment to 0 mg is not stated.

Conclusion:

The review does not identify any specific level of completion of tapering in OMT bur rather a range of 0% - 70 % dependent on selection for taper, characteristics of the population, type of motivation and approach in detoxification – excluding the not so relevant tapering under cover of anaesthesia that for other reasons is not recommended.

4.1.2 Follow-up period

The studies reviewed have varying follow-up periods. In some studies follow-up is limited to less than one week only focusing the completion of tapering. Several studies follow the samples for six months and some for several years. Relapses firsts month is mostly very high and all the first 6-12 months are characterized with a high relapse tendency. After three years relapses are infrequent (Cushman, 1978) but do nevertheless occur (Stimmel et al., 1977). A frequent observation is that situational factors are of high importance for the prevalence of relapse. This strongly indicates the importance of follow-up and the possibility to re-enter treatment.

Conclusion:

The review finds a widely differing period for follow up. A common sense conclusion supported by the unsystematic findings in the studies is that the initial period is particularly vulnerable and the first year is of high importance. However, after two – three years relapses become seldom but might nevertheless occur also after several years

4.1.3 Relapse to use of illegal opioids (abstinence rates)

The review from 2005 (Kornor & Waal, 2005) found 12 follow-up studies. There were considerable variations in definitions and assessment, but the authors nevertheless described a pooled abstinence

rate of 22 – 86 %. Of some importance is the finding that voluntary – "therapeutic detoxifications" had a pooled success rate of 48 % and were clearly superior to "non-therapeutic" with a pooled rate of 22 % . 10 years later another review focussing detoxification from buprenorphine maintenance therapy identified 10 relevant studies with duration of abstinence post taper 9,6 % - 50 % with follow-up time varying from 4 weeks to 11 weeks. Longer duration was associated with the use of naltrexone as relapse prevention (Bentzley et al 2015). The authors conclude that focus should be on retention in treatment – not on detoxification.

Some single studies are of particular significance. Eklund et al did a follow-up of 59 patients ever detoxified from MMT in Sweden, a program that encouraged indefinite treatment. 600 patients had been in treatment at the inclusion period, and thus 10 % had tried voluntary detoxification. 50 were reached for interview; 25 (5 %) had succeeded in long term abstinence after one to three attempts. 25 either did not succeed in completion of taper or returned to MMT (Eklund et al., 1994). Obviously taper is a possibility but few reach stable abstinence from opioids. Another Swedish study gives a similar picture (Hiltunen et al., 2011). The authors did a 15 years follow-up on the first 38 patients treated in Stockholm. 13 had no attempts to taper, eight had been forced to stop because of non-compliance, seven had successful and seven non-successful voluntary taper. The numbers are too small to give percentages, but the study indicates that taper might be a realistic possibility for a minority.

Larger population based studies indicate that successful taper on a rather low level. In the Nosyk study success was defined as taper below 5 mg methadone for the last 4 weeks of treatment without return to treatment, incarceration, mortality or opioid-related hospitalization the following 18 months (Nosyk et al., 2012). 646 taper episodes - 13 % - of the study sample fulfilled the criteria for successful taper.

Long term follow-up of treated samples tend to find discouraging results on detoxification. For instance Teeson found positive outcomes associated with time spent in maintenance therapy, residential rehabilitation and low number of treatment episodes but not with time spent in detoxification (Teesson et al., 2008).

Conclusion:

Relapse to illegal substance use is frequent and rates of enduring abstinence rather low. Due to small samples and/or indirect information, estimation of precise levels is not possible. From total samples in OMT treatment, the level of completed tapering is about 20 % but the level of successful tapering – enduring abstinence is found at half or less than half of this: 5-15 %.

4.1.4 Re-intake in OMT

As virtually all studies on OMT find increased rates of OD mortality and morbidity after OMT exit – particularly first month, emphasis is on easy re-intake. Prevalence of re-intake varies in different studies dependent on availability and program policy. Theoretical papers and policy recommendations underline the importance of availability of re-intake (Ksouda et al., 2013) (Bentzley et al 2015).

Conclusion:

Re-intake should be easily available after detoxification.

4.1.5 Mortality, criminal activity, morbidity and other unwanted events

Longitudinal studies uniformly find that OMT decreases unwanted events and that the prevalence increase post treatment – that is after detoxification (Bukten et al., 2012; Clausen et al 2008; Clausen et al., 2014; Ghodse et al., 2002; Goldstein & Herrera, 1995; Havnes et al., 2012; Magura & Rosenblum, 2001; Skeie et al., 2013; Teesson et al., 2008). The high risk period is in particular the first months, but risk also remains on high level later. However, tapering in settings with continued therapy such as therapeutic communities or other types of residential or rehabilitation units might improve (Ghodse et al., 2002). In contrast enriched detoxification do not seem to improve on results (Sorensen et al., 1984; Sorensen et al., 1992). The negative and unwanted events is largely related to relapse to drug use, and is not found in studies of clients who remain abstinent (Clausen et al., 2014; Eklund et al., 1994; Hiltunen et al., 2011; Riordan et al., 1976; Stimmel et al., 1977).

Conclusion:

Tapering and detoxification is followed by 1-3 months period with high level of unwanted events, and levels remain high, mostly on level with untreated samples also for a prolonged period after. The occurrence is however, linked to relapse to drug use and not found in groups that remain abstinent.

4.1.6 User satisfaction and changes in psychosocial functioning

This is in particular focussed on two Swedish projects (Eklund et al., 1994; Hiltunen et al., 2011). Compared to patients that do not taper from OMT and to patients not succeeding in taper, the abstinent group had increased level of psychosocial functioning and life satisfaction.

Conclusion:

User satisfaction and psychosocial functioning is seldom the focus in tapering studies, but are found increased in groups maintain abstinence in those that do focus these areas.

4.2 Do any specific elements/factors influence termination of OMT and tapering of OMT drugs?

4.2.1 Reasons and motivations for tapering – or not tapering

A British study found that 58 % of the clients in MMT had previously attempted self-detoxification with an average of 3.6 attempts per client. The reasons were in particular "for the family", "tired of the life style" (Noble et al., 2002). Another study found that 71 % of clients some time had tried to come of MMT or BMT (Winstocket al., 2011) A systematic qualitative study found the reasons typically connected to dissatisfaction with control measures or other program structure elements impeding or infringing on life style of life patterns. Other reasons were feelings of injustice or unfair treatment. Dissatisfaction with the agonist drug and/or longing for a drug free life is also prevalent (Reisinger et al., 2009). An US study found the same elements with disagreement with staff and infringement on life patters as the most important (Gryczynski et al., 2014). This study found however in addition that termination to a large extent was involuntary following missing days or urine findings indicating relapse. Another US study where patients had to finance treatment, found that costs of buprenorphine became too high and transportation to dispensing site too difficult (Bentzley et al. , 2015).

The latter study mainly found that clients usually want to continue in long term treatment. The reasons were fear of relapse to heroin use, fear of withdrawal symptom and satisfaction with the subjective experience of buprenorphine. The fear of withdrawal and of physical or psychological pain is important elements impeding motivation for taper. "Detoxification phobia" (Milby et al., 1990; Milby et al., 1994) and "abstinence fear" (Eklundet al., 1997) are anxiety reactions possibly developed after painful withdrawal episodes. Milby developed a questionnaire to detect withdrawal phobia, the Detoxification Fear Survey Schedule (DFSS) (Milby et al., 1987; Milby et al., 1986). Withdrawal might also – more seldom – be associated with development of psychosis (Levinsonet al., 1995), probably mainly in patients with pre-existing disorders or vulnerability. Depression might also represent a problem. Stable opioid-dependent patients undergoing detoxification from MMT might develop "characteristic mood changes" of dysphoric character (Kanof et al., 1993). The author even developed an assessment instrument, Profile of Mood States (POMS), to follow the development during tapering. A study of outcomes from Australia (ATOS) found that depression among heroin addicts was associated with more time in detoxification (Havard et al., 2006). These problems have not been focussed by other researchers. Nevertheless findings illuminates that patients in OMT often are vulnerable for mental health problems and might develop illness during stressful tapering. There might be an important interrelationship between affective states and development of protracted withdrawal (Latowsky, 1996).

Conclusion:

The desire to terminate OMT is common among OMT clients, often but not only caused by restrictive program characteristics. Negative motivations might be associated with drop-out and unfruitful self-detoxification episodes. Disciplinary staff reactions might also be causative. Programs should take care to counteract negative motivations and stimulate problem-solving discussions. One should also be aware of possible anxiety states and depressive tendencies and also the possibility of psychosis in vulnerable individuals.

4.2.2 Consequence of type of termination of OMT / Voluntary versus involuntary tapering

Several longitudinal studies indicate that the termination of OMT initiates a period of increased mortality, morbidity and criminality (Clausen et al., 2008; Clausen et al., 2014; Cousins et al., 2011; Ghodse et al., 2002; Gossop et al., 2001; Magura & Rosenblum, 2001; Skeie et al., 2013; Teesson et al., 2008). Disciplinary termination should therefore not be an easy choice and in always followed by systematic tapering (Ksouda et al., 2013). However, while disciplinary termination should be avoided, the usual problem is dropout. The patients solve the problems either by non-attendance at dispensing sites or by incarceration. Termination is therefore usually a consequence of unsuccessful treatment, by clients wanting to continue drug taking or by high level criminal activity and almost by definition linked to negative consequences.

These considerations are also relevant for the comparison between voluntary and involuntary tapering of OMT drugs. By definition non-voluntary treatment is associated with non-compliance, disciplinary problems, non-attendance at dispensing sites and clients negative to the OMT program.

Voluntary tapering might also be a choice for individuals that dislike aspects of the OMT programs but nevertheless they usually have an ongoing collaboration with staff. They might also initiate tapering because they desire a life without drug use or at least without necessity of adapting to program requirements. More often voluntary tapering is associated with high level psychosocial rehabilitation and low level of ongoing drug use within program. These aspects cause the prognosis to be different and there are almost no studies comparing voluntary and involuntary tapering. The studies all focus voluntary tapering and are often coined “therapeutic tapering”.

Conclusion

Termination of OMT is in general associated with increase in negative outcomes and should only be encouraged on voluntary basis. Involuntary termination of OMT is associated with high level of conflict in OMT and dissatisfaction with program elements, often causing disciplinary staff reactions and decisions. Nevertheless medically sound tapering should be offered. As there are no systematic studies, the evaluations are based on common sense considerations.

4.2.3 Importance of degree of drug free states and social rehabilitation (recovery)

It follows from the paragraph above that rehabilitation including low level of drug use is emphasized when clients are selected for voluntary tapering. This creates a systematic selection towards high lever function and low level drug use. Some studies have tried to investigate the elements that influence tapering by comparing successful with not successful groups. A pattern for instance found by Eklund is that the those who terminate successfully live alone more seldom at follow-up, have more often children and live more often in own housing versus institution and have a higher level of vocational independence (Eklund et al., 1994). However, the numbers in the study are too small to allow for calculations of significance.

Conclusion:

Few systematic studies focus the importance of recovery as such. However, a few studies find recovery in treatment to favour voluntary tapering and a few studies find higher level of elements in recovery in former patients that stay abstinent. Recovery is associated with higher level of quality of life. The conclusions are supported by a few small studies – and by common sense.

4.2.4 Differential problems and/or results according to type of agonist involved?

Tapering from OMT meets the same type of problems as found in reviews of OMT and reviews on tapering. The withdrawal symptoms increases during methadone tapering and gets worse when doses are lower than 40 mg, in particular form 30 mg and even more below 20 mg. Cognitive problems might be found after long term MMT and to a less degree after BUP. It is not clear whether this is associated with complications to the degree and seriousness of earlier heroin addiction and drug life or to the maintenance drug. The finding of affective states, anxiety reaction and development of psychotic symptoms has been done in studies of methadone tapering. Tapering from methadone might have some higher level of mortality risk. Tapering from BMT meets with withdrawal symptoms in particular when below 8 mg and increases below 4 mg and in particular below 2 mg.

Conclusions

The tapering from MMT and from BUP meet with the same type of withdrawal symptoms. There are some findings that indicate less severe problems after BUP. However, it is not established that there are differential results.

4.2.5 Recommendations for specific tapering regimes and procedures (duration, user influence)

Tapering regimes are investigated in a few RCT studies but with differing target populations, agonists used and follow up measures. Compiling of findings is not possible. Tennant & Shannon compared decreasing daily single dose methadone with propoxyphene with methadone delivered twice daily (Tennant & Shannon, 1978). The results were comparable and both superior to clinical experience with ordinary methadone tapering. Kleber compared abrupt detoxification from 20 mg methadone clonidine with gradual 1 mg decreasing dose of methadone (Kleber et al., 1985). The same level reached completed tapering but the clonidine group experienced withdrawal early and the methadone group late in the process. Kleber concludes that clonidine is a safe alternative in final stage of MMT termination. Janiri compared detoxification from MMT by use of lefetamine (a stimulant drug with analgesic effects), clonidine and buprenorphine (Janiri et al., 1994). Buprenorphine was significantly superior to the other drugs in controlling withdrawal symptomatology. Sees et al compared MMT to 180-days "psychosocially enriched" detoxification treatment (Sees et al., 2000). MMT were superior in reduction of heroin use and HIV risk behavior. Gruber et al compared standard MMT, MMT with minimal level counselling and 21-day methadone detoxification (Gruber et al., 2008). Even with minimal counselling heroin and alcohol use was reduced more by MMT than by detoxification. An Australian study on transfer from methadone to buprenorfin compared transfer at fixed dose (30-40 mg methadone) to transfer "when uncomfortable". Both approaches were acceptable. All patients were stabilized on buprenorfin and slowly tapered from 4 mg to 0 mg (Breen et al., 2003). One US study focused incarcerated MMT patients to be released randomized to two groups. One had continued MMT and the other forced (involuntary) tapering in prison and reengagement the first month after release. At follow up the first group had significantly higher percentage in treatment in community based MMT, less use of heroin and better adjustement (Rich et al., 2015). One study compared tapering with slow-release oral morphine (SROM) with methadone for voluntary inpatient detoxification from maintenance treatment to abstinence (Madlung-Kratzeret al., 2009). SROM was found (non-inferior) to methadone meaning that withdrawal problems measured by SOWS and percentage fulfilling tapering were on same level. Some single studies without control technology give additive knowledge. Banbery investigated dihydrocodeine in a small British study and found the approach useful (Banbery et al., 2000).

The search has not revealed projects evaluating duration of tapering or user influence. There is some indirect evidence that slow tapering with stabilizations periods might be beneficiary, particularly for clients stabilized on higher dose levels. There is also some evidence that the last slow stage might be completed in less than three weeks. All systematic studies are performed on clients in voluntary detoxifications, mostly with possibility for the clients to decide for pauses in tapering or to revert to earlier dose levels. From general studies on opioid detoxification it is known that relapse prevention with antagonists, in particular slow release types, is recommendable. The same is obviously the case with patients tapering from OMT.

This research largely confirms general knowledge on detoxification in opioid dependency. Continued maintenance treatment is superior to detoxification measured by relapse to heroin use and probably also by low level HIV risk behavior, mortality and morbidity, but varying methodology and target behaviors prevents met-analysis and estimation of effect level. The conclusions are when graded, on level 3 to 4 and to a large extent dependent on support from evaluations on basis of clinical experience.

Conclusions:

It is reasonable to state that alfa-adrenergic agonists are useful in alleviating withdrawal symptom in detoxification from OMT but even so, opioid tapering increases the percentage fulfilling detoxification. There is no specific reason to use other opioid agonist than methadone or buprenorphine even if SROM seems on par with methadone. Codeine and other opioid agonist are possible but not well supported alternatives. Withdrawal from BMT is probably somewhat easier than from MMT, and there are some indications that symptoms after methadone tapering are more protracted. The inference is suggestions that MMT patients might benefit from a change to buprenorfin after a taper to 20-30 mg. Slow taper with small dose reductions is however also possible with use of methadone below 20 mg. Slow taper with buprenorfin is particularly important below 4 mg. Protected/controlled environment is often important in the final stage of tapering. Outpatient detoxification is possible, but the patients need more support and control in the last stages than often available in outpatient settings. Relapse prevention by supported milieus and/or opioid antagonists is recommendable.

4.3 Prognostic factors influencing success in tapering and prevalence of relapse to use of heroin.

Few studies focus this question. Langrod hypothesized that “internal locus of control” would make the patient more likely to want detoxification and to actually initiate the process. The finding was that those with internal locus actually were more willing to plan for the process but less willing to start the tapering (Langrod et al., 1983). Capone tried to investigate client variables associated with outcome in a tapering program. None of the selected variables were found to differentiate (Capone et al., 1994). Eklund found that the type of interventions has bearing on level of success while few conditions (patient variables) seemed to make systematic difference (Eklund et al 1995). Latowsky emphasizes the affective states of the patient and warns against associated protracted withdrawal with high risk of relapse (Latowsky, 1996). A similar finding is underlined by Kanof who states that “organic mood syndrome” is associated with poor prognosis (Kanof et al., 1993). Milby found detoxification phobia – strong fear of withdrawal symptoms to be a barrier to start tapering (Milby et al., 1994). Winstock finds that if the staff do not furnish opportunities for voluntary tapering and are unobservant of the patient’s wishes to come off, a higher percentage will “jump of”- try to detoxify

by themselves with small chances of success (Winstock et al., 2011). Ksouda identifies studies of successful tapering to be associated with stable clients with a wish for a life without maintenance treatment (Ksouda et al., 2013).

Conclusions:

Research directly focusing prognostic factors for successful tapering and stable post taper abstinence is scarce. It is however, considerable data indicating the importance of voluntariness and planning. The benefits of drug free life should be realistically in sight. Further, taper is associated with considerable discomfort that might be combined with anxiety reactions or development of affective disturbances. The chances of goal attainment seem to be considerably increased when patients are a partner in planning and monitoring tapering. Withdrawal might be increased in patients with high level long standing OMT, and less in patients with a shorter drug using period. Some studies indicate that abstinence post taper is strongly influence by the type of milieu and relationships that meet the sober patient. Integrating taper with therapeutic milieus or self-help groups has been advocated but research is scarce.

5. FUTURE RESEARCH

1. Cohort and populations studies with long term follow-up of OMT after treatment. The Norwegian OMT program has presently 7600 in treatment. 12000 have at some time been involved. A study program combining register studies with selective case finding might give important information.

2. Prospective studies of patients actively opting for tapering with individual data on personal resources, psychosocial situations and individually structured treatment programs. The studies might focus availability of self-help support, therapeutic programs and exit strategies. If possible the study should include controlled comparisons between treatment with and without slow release antagonist relapse prevention.

3. Neurobiological studies on level of neuroplastic changes in relation to tapering and post taper functioning. If possible the study should include genetic analysis investigating vulnerability and resilience.

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