No harm and some benefit in letting methadone patients choose their dose. user involvement self-regulation client choice dose

Nugget 7.5

No harm and some benefit in letting methadone patients choose their dose

Findings Methadone maintenance patients allowed to set their own doses do not escalate to excessive levels and there may be benefits in terms of improved patient-therapist relations and reduced illicit drug use.

A US maintenance clinic for opiate addicts where a doctor's approval was required before methadone doses could be increased to 100mg or more a day decided to waive this requirement for all existing and new patients, allowing patients themselves to decide to increase (or decrease) their doses with no pre-set limits. Other features of the regimen were unchanged. These included a phased relaxation of the initial requirement to attend six times a week to consume methadone at the clinic so long as patients remained more or less abstinent from illicit drugs and attended counselling and group therapy sessions, monthly urine testing for illicit drug use and to check whether methadone has been taken, random recall of patients to the clinic to check that they still had the take-home doses they had been prescribed, and a limit on methadone increases of 5mg maintained for at least four days before further change. About half the monthly caseload at the clinic were in treatment for at least six months before the change and for 16 months afterwards. Three quarters of these 57 patients were stable and compliant enough to have progressed to infrequent attendance requirements over at least three years at the clinic. Even before the change, very few of their urine tests were positive for opiates and just 1 in 10 or less for any other illicit drug. Afterwards there was a significant drop from 5.26% to 1.64% opiate positive tests and no change with respect to other illicit drugs. No patient failed to show possession of recalled take-home doses, and enforcement services recorded no instances of liquid methadone diversion. Retention periods and discharge rates were unchanged. The average methadone dose increased significantly but only very slightly from 77mg to 80mg, partly due to

the one or two patients[1] who for a short time tried doses of up to 300mg. Nearly 90% of patients made do with doses of 100mg or less.

In context Effectively this was a study of how mainly stable, long-term methadone patients already on relatively high average doses respond when the ceiling is lifted on the daily methadone dose they can choose to gradually move up to. From this and from previous studies it seems clear that patients allowed to set their own dose levels will generally not do so to excess, that retention and outcomes will not suffer, and that patient satisfaction and client-treatment relations may improve. It is also the third study to have shown that such a regime leads to reduced illicit drug use. But these findings generally relate to very specific conditions. Studied regimes have allowed doses to be increased only by small steps set several days apart in order to be able to assess the impact of each increase and to minimise overdose risk. Patients have been closely monitored to ensure that methadone is taken as prescribed and neither hoarded nor diverted on to the illicit market, removing one incentive for upping the dose beyond the level dictated by the individual's daily needs. Usually, too, a limit has been set to how much will be prescribed per day and above a certain point take-home doses have been withdrawn, a disincentive to increase the dose beyond this point. What the featured study shows is that when the other controls are in place and for stable patients, a limit on dose levels can be waived without undue escalation or diversion of methadone on to the illicit market. This and other studies have also indicated that when other anti-diversion controls are retained, there is also no need to automatically bar take-home doses beyond a certain dose level. Taken together, studies to date indicate that patient self-regulation of dose is beneficial compared to an inflexible dose regime or one with a bias towards minimising doses, but not when compared to flexible regimes which aim to maximise outcomes and client functioning and comfort rather than to minimise doses.

In the featured study how less stable patients would have responded remains an open question, though the authors do comment that just one other patient at the clinic increased their dose to 300mg and there was no evidence of diversion even among what on average were less compliant and/or less long-term patients.

Practice implications So long as measures are in place to minimise overdose risk and to prevent diversion of medication on to the illicit market, allowing patients to regulate their own dose in consultation with their key worker does not lead to excessive doses and removes a potential source of friction between patients and staff. An added potential benefit is that self-regulation insulates patients from changes in clinic personnel and policies which might otherwise have led to disruptive fluctuations in dose. There seems no reason why this type of regime should not be implemented for new or established stabilised patients. However, if the alternative is an almost equally flexible regime within which the patient's response is a significant element in dosing decisions, little is gained in terms of retention or outcomes. On the other hand, patients at clinics where doses are set inflexibly, especially when these tend to be too low, will do less well than patients in flexible dosing regimes which allow doses to rise in response to individual need. Whether the flexibility is nominally in the hands of staff or the patients is less important. If it is the latter, medical staff must maintain a monitoring role and cannot divest themselves of the responsibility to step in if the patient is thought to be acting against their own medical interests. Given continued careful monitoring and limits on how quickly

doses can be changed, such occasions will be rare. Any regime which allows doses to rise to high levels should consider intensified monitoring of patient compliance and response to medication at higher doses. Staff in patient-regulated regimes may still wish to set a limit (eg, 120mg[2]) beyond which the decision reverts to the doctor and/or objective indicators of need (low plasma levels of methadone, physical withdrawal symptoms) are required. Such a regime would almost certainly improve outcomes at British methadone services which generally under-prescribe in relation to national and international guidelines.

Featured studies Robles E. *et al*. "Implementation of a clinic policy of client-regulated methadone dosing." *Journal of Substance Abuse Treatment*: 2001, 20, p. 225–230. Copies: apply DrugScope.

Additional reading Ward J., *et al*, *eds*. *Methadone maintenance treatment and other opioid replacement therapies*. Harwood Academic Publishers, 1998. Copies from bookshops.

Contacts Elias Robles, Substance Abuse Treatment Clinic, University of Arkansas for Medical Sciences, 4301 West Markham Street, Slot 611-1, Little Rock, AR 72205-7199, USA, fax 00 1 501 686 9637, e-mail RoblesSoteloElias@exchange.uams.edu.

Thanks to Andrew Preston of Exchange Health Information for his comments.

Links *Nugget* **5.9**

Nugget 7.5. Appendix of notes for In context section

About the study

Strengths of the study include the fact that the research was based on what seem to have been excellent and practically complete clinic urinalysis records and did not interfere with normal treatment processes. Patients were not interviewed or assessed for research purposes, nor was there any selection of patients for the study other than the retention requirement. These features give confidence in the applicability of the results to everyday practice with similarly stable, long-term patients. The restriction to just one take-home dose for patients on 100mg or more of methadone was not applied in the self-regulation condition; if it had been it would have acted as a strong deterrent to exceeding this limit, since for most patients it would have entailed another five daily visits to the clinic. That despite this patients were restrained in their dosing decisions is all the more impressive. How less stable patients would have responded remains an open question, though the authors comment that just one other patient at the clinic increased their dose to 300mg and that there was no evidence of diversion even among what on average were less compliant and/or less long-term patients.

Flexible prescribing and self-regulation of dose in methadone programmes

This review was prepared as background notes for Nuggets published in Drug and Alcohol Findings. It is not intended to be a systematic review based on an extended search for relevant research but to be sufficient to support the published article.

This review details evidence that methadone patients allowed to set their own doses will generally not do so to excess, that retention and outcomes will not suffer, that patient satisfaction and client-treatment relations may improve, and that such a regime can reduce illicit drug use. Taken together, studies to date indicate that patient self-regulation of dose is beneficial compared to an inflexible dose regime or one with a bias towards minimising doses, but not when compared to flexible regimes which aim to maximise outcomes and client functioning and comfort rather than to minimise doses.

The findings generally relate to very specific conditions. Studied regimes have allowed doses to be increased only by small steps set several days apart in order to be able to assess the impact of each increase and to minimise overdose risk. Patients have been closely monitored to ensure that methadone is taken as prescribed and neither hoarded nor diverted on to the illicit market, removing one incentive for upping the dose beyond the level dictated by the individual's daily needs. Usually, too, a limit has been set to how much will be prescribed per day, and above a certain point take-home doses have been withdrawn, a disincentive to increase the dose beyond this point.

These limitations have been imposed as safeguards against potential abuse rather than in reaction to experience indicating that without them patients actually do abuse the system. Several studies have indicated that some are unnecessary. One US study found that, when other controls are in place and for stable patients, a limit on dose levels can be waived without undue escalation or diversion of methadone on to the illicit market.[3] This and other studies have also indicated that when other anti-diversion controls are retained, there is also no need to automatically bar take-home doses beyond a certain dose level.[4 5]

Practice implications

So long as measures are in place to minimise overdose risk and to prevent diversion of medication on to the illicit market, allowing patients to regulate their own dose in consultation with their key worker does not lead to excessive doses and removes a potential source of friction between patients and staff. An added potential benefit is that self-regulation insulates patients from changes in clinic personnel and policies which might otherwise have led to disruptive fluctuations in dose.

There seems no reason why patient self-regulation should not be implemented for stabilised patients. However, if the alternative is an almost equally flexible regime within which the patient's response is a significant element in dosing decisions, little

is gained in terms of retention or outcomes. The key factor is *flexibility* of dosing in response to the patient's needs and reactions to the current dose. Whether this flexibility is in the hands of the doctor or the patient is less important. If it is the latter, medical staff must maintain a monitoring role and cannot divest themselves of the responsibility to step in if the patient is thought to be acting against their own medical interests. Given continued careful monitoring and limits on how quickly doses can be changed, such occasions will be rare.

Any regime which allows doses to rise to high levels should consider intensified monitoring of patient compliance and response to medication at higher doses. Staff in patient-regulated regimes may still wish to set a limit (eg, 120mg[6]) beyond which the decision reverts to the doctor and/or objective indicators of need (low plasma levels of methadone, physical withdrawal symptoms) are required. Such a regime would almost certainly improve outcomes at British methadone services which generally under-prescribe in relation to national and international guidelines.

The importance of adequate doses

In the English NTORS study,[7] for 240 patients the initial treatment plan was methadone maintenance (stable non-reducing dose, usually for at least six months) and for 111 methadone on a reducing basis over what was generally an unspecified period,[8] though rarely a month or less. Among patients intended to receive maintenance, at two years those retained in the original programme were half as likely to be regularly using heroin as those who had left, and each mg more methadone they received per day was associated with a 2% reduction in the chances of regular heroin use.

In British methadone maintenance treatment doses average about 50mg daily and just a quarter of patients receive over 60mg,[9] the dose identified in UK national guidelines as the lower end of the range which produces greatest benefit.[10] The generally low doses seen in Britain are a concern because higher doses of methadone (either on average for each patient, on average for each clinic, or in studies which test one dose against another) generally result in better retention and better outcomes[11 12 13] and may even improve the chances of eventual successful withdrawal from methadone.[14] In one study raising the dose for all patients from about the average seen in Britain (50mg) by just 20mg substantially improved heroin use outcomes.[15] Where higher doses are not associated with better outcomes, the reason may be that more severely affected patients (including those with HIV) are selected for higher doses.[16]

However, the absolute number of mg per day is probably less important than titrating this to the optimal level for each individual. Someone already functioning well on 40mg a day will not improve if the dose is doubled, but someone functioning poorly may well do so. A few do well on 0mg of methadone in the form of a placebo.[17] Individualisation of dose is important partly because individuals differ widely in the blood levels reached after the same dose of methadone.[18] Where levels are low, increasing the dose may eliminate heroin use.[19 20]

The importance of flexible, individualised dosing

A few studies have compared flexible, individualised dosing to more standardised regimes. In one US report clinics which appeared to prescribe flexibly (judged by the range of dose levels) had better retention than clinics with a restricted dose range.[21] Another US report studied what happened when doses were raised for 164 patients already receiving 100mg methadone a day but who were still unable to control their heroin use. Doses were individually increased until each patient no longer felt discomfort and rarely supplemented their medication with heroin. At an average of 211mg a day, heroin use was virtually eliminated.[22] In Italy a methadone clinic which specialised in patients who had not responded to treatment elsewhere was able to increase doses individually to the point where supplementary heroin use was very infrequent. For patients without psychiatric complications, this averaged 99mg but for those with diagnosed mental illness it averaged 154mg.[23] In clinics where such increases are not considered or where illegal drug use is punished with a dose reduction, these US and Italian patients would have continued to have been seen as treatment failures.

There is now a substantial body of evidence that flexibility in dosing rather than the absolute level is the key factor. When doses are allowed to rise (or fall) to individually appropriate levels, the absolute level of the dose has been found to no longer predict how long individuals stay in treatment[24 25 26] or how well they do,[27 28 29 30] and the service's overall retention record may be higher than is typical in less flexible services.[31 32] Relatively high dose levels in a clinic may be less important in themselves than as a sign that the clinic is prepared to allow doses to rise in response to individual need. Low average doses across a caseload may be symptomatic of a reluctance to allow doses to rise to these levels (possibly due to a cure/abstinence rather than a harm reduction orientation[33]), resulting in poorer retention.[34] Independently of the average dose each client received, one study found that clinics which reacted constructively to patients' problems had better retention; increasing the dose was the most common of these responses.[35] In Amsterdam, high stable doses of methadone were not significantly related to whether addicts stopped injecting, but steadily increasing doses were.[36] In the Dutch context we can speculate that high doses were unrelated because these were prescribed to people precisely because they were at high risk of continuing to inject. Dutch methadone services generally restrain methadone dose levels to permit continued heroin use.[37] Their concern is that 'blockade' level prescribing which effectively deprives patients of the 'pleasures' of heroin will also deprive clinics of their patients. In this context a more measured approach, gradually increasing doses in response to continued injecting-related risks, appears to have led to a gradual reduction in the frequency of injecting and eventually to its cessation.

Achieving individualisation and flexibility through patient self-regulation

Fewer still studies have investigated flexible dosing regimes which allow the patient to determine the dose.[38] We'll consider their findings one by one, bearing in mind a

potentially important difference between them. Studies 1 and 2 effectively penalised patients who opted to increase their doses over a certain level (50mg or 100mg) by withdrawing take-home privileges, and rewarded patients who opted to dip below this line by making them eligible for such privileges. Given the value patients attach to take-home doses (the reason why they are used as a reward for encourage drug-free urines), such studies are not an untrammelled test of whether patients allowed to increase their dose will do so to excess. Studies 3, 4 and 5 avoided this confounding influence.

A respected review of methadone and other maintenance treatments took in studies 1, 2 and 3 and summarised their findings as follows: "In conclusion, there seems little basis to the fear that if patients are given control over their own methadone dose they will raise it irresponsibly in an attempt to achieve intoxication. It has to be emphasised, however, that these studies had constraints in place to guard against the possibility of overdose. With regard to illicit drug use, it appears that self-regulation is no better or worse that standard procedures for the setting of doses. Self-regulation may, however, independent of its effect on illicit drug use, contribute to the process of methadone maintenance by enhancing patient trust and responsibility and this outcome is worthwhile in and of itself."[39] The later studies 4 and 5 support this view and indicate that some of the constraints thought necessary in the earlier studies can be dispensed with.

Study 1 In 1973 a US methadone clinic switched for six months from about 50mg a day for virtually all maintenance patients (set by staff and not divulged to patients) to an open-dose, self-regulation policy which allowed patients to change their dose up or down once a week by 5mg up to a maximum of 120mg.[40] If the dose at any time exceeded 50mg take-home privileges were withdrawn. Data from the five weeks before the change provided a baseline. During the study the caseload fluctuated from 76 to 99 patients. Overall the typical dose (median) rose by just 10gm. Though six months gave plenty of time for escalation to the 120mg maximum, at any one time only two patients opted for this dose and by the end three-quarters were on 70mg or less. Among the 59 patients in treatment from the start of the study, there was some indication that those with take-home privileges to lose stuck at 50mg, and only one chose to go further, but most who could have pushed up to this level did not. Patients without take-home privileges had nothing to lose from escalating to 120mg but most stayed at 50mg or less and the rest tended to cluster towards the bottom end of the 50–120mg range. In other words, few patients pushed their dose to the absolute limit and only a minority to the take-home limit. Among these same 59 patients, the 18 who increased their dose tended to produce fewer opiate positive urines as the dose went up and had significantly fewer than at baseline, a trend not seen among the remaining patients. All the patients surveyed at the end of the study preferred to be able to control their dosage and staff too preferred this regime.

Study 2 A randomised controlled trial at two US clinics tested standard treatment against two self-regulation conditions.[41] Standard treatment at this clinic generally meant an attempt to limit doses to the lowest possible level. 116 clients agreed to take part in the trial; all but seven completed 16 weeks of treatment and were included in the analyses. All had earned at least one take-home dose. Doses at the start averaged 46mg a day. No patient could exceed 120mg. In both self-regulation conditions, changes were limited to 10mg once a week and clients on over 100mg forfeited any take-home privileges. In one of the self-regulation conditions take-home doses were offered as a reward for lowering doses. Though this made little difference to dose levels, results from this group are excluded in the following account.

At one of the clinics self-regulation patients on a maintenance (as opposed to reduction) regime who had some 'room' left to substantially increase their dose (ie, starting dose 46–65mg) did so for a few weeks but then fell back towards the overall mean. At the other clinic average doses fell over the course of the 16 weeks to roughly the same degree in all the groups. Illicit opiate use as revealed in weekly urinalyses tended to be lower (at one stage, significantly so) among the self-regulation patients.

Patients at the first clinic were followed up for another 32 weeks.[42] Over this longer scale the initial bump upwards in doses among self-regulation patients can be seen as transitory and of little clinical significance, and doses remained essentially stable. The same was not true of the patients (specifically the women) whose dosage was under clinic control, a finding the authors speculatively attribute to organisational strains at the time in the clinic. It seemed that the ability of self-regulation patients to divorce dosage decisions from these strains contributed to their stability. In every four-week period over the 48 weeks of the study self-regulation patients consistently produced fewer opiate positive urines, and over the entire period this was statistically significant. For example, at 24–32 weeks about 4 in 10 of the urines produced by standard care patients were opiate positive compared to 1–2 in 10 among self-regulation patients. Retention in treatment was high and unaffected by self-regulation.

Study 3 At a community addiction treatment centre 200 patients seeking methadone maintenance treatment were equally and randomly allocated for a year either to standard treatment with doses set by the patient's doctor or to a treatment which allowed patients to regulate their methadone dose.[43] No exclusion criteria were applied which would significantly affect generalisability to all patients at the clinic. All patients were counselled twice a week. In the standard treatment patients on over 60mg could not qualify for regular take-home doses, a limitation waived in the self-regulation condition. In the latter condition 100mg was the maximum dose[44] and doses could be increased by up to 10mg once a week. Virtually all the

patients were interviewed a year after starting treatment to assess outcomes. Maximum average methadone dose was only slightly and insignificantly higher in the self-regulated group (58 v 53mg), largely due to more patients opting for doses of 80mg or more (15 v 6 patients). In both conditions half the patients were retained continuously in treatment for a year after which they all returned to standard treatment. The reversion to clinic-regulated dosing did not lead to greater drop out among patients previously able to set their own dose (about a fifth were retained in both conditions), possibly because by then they had achieved their optimal level. Among the half of patients retained for a year neither illicit drug use nor crime or HIV risk behaviour differed across the treatments. Though clinic policy meant no patient was thrown out for illicit drug use or crime, at one year these were at very low levels. The authors speculate that the lack of impact of self-regulation was partly due to patients in the standard treatment also perceiving a large degree of control over their dose, presumably because this was flexibly adjusted in response to feedback from the patients. In support of this interpretation, though the number of dose changes was significantly higher when chosen by the patients, the difference was small and both groups averaged about one change a month. It seems that when doctors are in any event flexible and responsive, limits are set to how quickly and how much patients can increase the dose, and patients are closely monitored, self-regulation makes little difference to retention, outcomes, or average dose levels, even when there is nothing to be lost from pushing one's dose to the limit allowed.

Study 4 Another US study also concluded that average methadone doses did not increase under self-regulation.[45] In this study there was no penalty in terms of loss off take-home privileges for increasing dose above a certain level. At a methadone clinic all stabilised patients on at least 20mg were given the option of changing their own dose at the next visit by up to 10mg a week in one or two steps a week. Over 32 weeks just under half took advantage of this opportunity, mostly to increase their dose. But over the course of the study increases averaged a modest 10–13mg and a fifth of patients decreased their doses by about the same amount. The minority of patients who opted to continue to seek a doctor's approval for a dose change did so in order to have it implemented immediately rather than out of preference for this method. Just under half the patients did not ask for their dose to be changed using either method. The net result was that average doses remained unchanged at 60mg over the 32 weeks. Before the shift to self-regulation this clinic was already operating a flexible dosing regime and approved most patient requests, but the process entailed considerable staff time and some frustration for patients who had to wait to see a doctor. The justification for this process was to prevent clinically contraindicated dose levels. However, none of the self-regulated doses went beyond clinically appropriate levels. Given this experience, the more streamlined method of simply doing what the patient asks within certain limits and continuing to monitor reactions was made standard practice at the clinic.

Study 5 The most recent study and one of the most significant was set in a US methadone maintenance clinic where a doctor's approval was required before doses could be increased to 100mg or more a day. The clinic decided to waive this requirement for all existing and new patients, allowing patients themselves to decide to increase (or decrease) their doses with no pre-set limits.[46] Other features of the regime were unchanged. These included: a phased relaxation of the initial requirement to attend six times a week to consume methadone at the clinic so long as patients remained more or less abstinent from illicit drugs and attended counselling and group therapy sessions; monthly urine testing for illicit drug use and to check whether methadone has been taken; random recall of patients to the clinic to check that they still had the take-home doses they had been prescribed; and a limit on methadone increases of 5mg maintained for at least four days before further change.

About half the monthly caseload at the clinic were in treatment for at least six months before the change and for 16 months afterwards. Three-quarters of these 57 patients were stable and compliant enough to have progressed to infrequent attendance requirements over at least three years at the clinic. Even before the change, very few of their urine tests were positive for opiates and just 1 in 10 or less for any other illicit drug. Afterwards there was a significant drop from 5.3% to 1.6% opiate positive tests and no change with respect to other illicit drugs. No patient failed to show possession of recalled take-home doses, and enforcement services recorded no instances of methadone diversion. Retention periods and discharge rates were unaffected. The average methadone dose increased but only very slightly from 77mg to 80mg, partly due to the one or two patients[47] who for a short time tried doses of up to 300mg. Nearly 90% of patients made do with doses of 100mg or less.

Effectively this was a study of how mainly stable, long-term methadone patients already on relatively high average doses respond when the ceiling is lifted on the daily methadone dose they can choose to gradually move up to. Strengths of the study include the fact that the research did not interfere with normal treatment processes and was based on what seem to have been excellent and practically complete clinic urinalysis records. Patients were not interviewed or assessed for research purposes, nor was there any selection of patients for the study other than the retention requirement. These features give confidence in the applicability of the results to everyday practice with similarly stable, long-term patients. The restriction to just one take-home dose for patients on 100mg or more of methadone was not applied in the self-regulation condition. If it had been retained it would have acted as a strong deterrent to exceeding this limit, since for most patients it would have entailed another five daily visits to the clinic. That despite this patients were restrained in their dosing decisions is all the more impressive. How less stable patients would have responded remains an open question, though the authors comment that just one other patient at the clinic increased their dose to 300mg and that there was no evidence of diversion even among what on average were less compliant and/or less long-term patients.

Contribution to good client-counsellor relationship

As already cited above, another way self-regulation might improve methadone treatment is by "enhancing patient trust and responsibility."[48] There is persuasive evidence that a good therapeutic relationship between methadone clients and their counsellors and the discussion of a range of health and drug-related topics during counselling contribute to retention and outcomes.[49 50 51 52 53 54 55] Dosing decisions can be a major source of friction between staff and methadone clients, impede open communication and act as a distraction from the rehabilitation process.[56] By sidestepping the possibility of such conflict, self-regulation could contribute to the development of a therapeutic relationship and free time for more productive exchanges. If so, it can be expected to play its part in improving outcomes through this mechanism as well as through any direct pharmacological effect.

The kind of counterproductive tensions sidestepped by patient self-regulation were illustrated in a study of methadone clinics in Britain.[57] Clients who feared that illegal drug use would meet with a disciplinary reaction and possible dose reduction reacted by withholding information, creating distrust and tension. Some key workers tried to avoid such conflict by distancing themselves from decisions over dose. In another report from the same study staff tended to emphasise the importance of involving clients in decisions over their treatment including dose in order to safeguard or create a good relationship.[58] Getting 'bogged down' in negotiations over dosage was seen as a distraction from productive counselling or therapy. Where withholding of information by the client, distancing by the keyworker, or poor staff-client relationships, impair the ability of staff to adjust dosage and other features of treatment in response to continuing illegal drug use, the likely result is a reduction in the effectiveness of methadone treatment.[59 60]

When British methadone patients[61] were asked how doses should be decided the top method (55%) was mutual consent and the least preferred was imposition by staff (1%).[62] About a third favoured response to client requests and the same proportion or more favoured objective methods which would effectively titrate dose to individual need. Flexibility in response to individual need was a major emphasis in their vision of the ideal methadone service.

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1 Woody G.E. "A commentary on 'Implementation of a clinic policy of client-regulated methadone dosing'." *Journal of Substance Abuse Treatment*: 2001, 20, p. 231.

2 Department of Health, Scottish Office Department of Health, Welsh Office, Department of Health and Social Services Northern Ireland. *Drug misuse and dependence – guidelines on clinical management.* HMSO, 1999. Higher doses are considered justifiable only in exceptional cases.

3**.** Robles E. *et al.* "Implementation of a clinic policy of client-regulated methadone dosing." *Journal of Substance Abuse Treatment*: 2001, 20, p. 225–230.

4**.** Maddux J.F *et al.* "Patient self-regulated dose and optional counseling in methadone maintenance." *American Journal of the Addictions*: 1995, 4(1), p.18–32.

5**.** Resnick R.B. *et al.* "Patient self-adjustment of methadone maintenance dose." In: Harris L.S. *ed. Problems of drug dependence.* NIDA, 1981, p. 327–330.

6**.** Department of Health, Scottish Office Department of Health, Welsh Office, Department of Health and Social Services Northern Ireland. *Drug misuse and dependence – guidelines on clinical management.* HMSO, 1999. Higher doses are considered justifiable only in exceptional cases.

7. Gossop M. *et al.* "Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study." *Drug and Alcohol Dependence*: 2001, 62, p. 255–264.

8. 1% month or less, 30% over a month, leaving presumably 69% for whom this information was not available.

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10. Department of Health etc, op cit.

11. Ward J. *et al.* "Methadone maintenance therapy for opioid dependence." *CNS Drugs*: 1996, 6(6), p. 440–449.

12. Ward J. *et al.* "The use of methadone during maintenance treatment: pharmacology, dosage and treatment outcome." In: Ward J., Mattick R.P., Hall W., *eds. Methadone maintenance treatment and other opioid replacement therapies.* Harwood Academic Publishers, 1998, p. 205–238.

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22. Maxwell S. *et al*, op cit.

23. Maremmani I. *et al.* "Methadone dose and retention during treatment of heroin addicts with axis I psychiatric comorbidity." *Journal of Addictive Diseases*: 19(2), p. 29–41.

24. Maddux J.F. *et al*, op cit.

25. Blaney T. *et al.* "Methadone maintenance: does dose determine differences in outcome?" *Journal of Substance Abuse Treatment*: 1999, 16(3), p. 221–228.

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