Erectile dysfunction: is the NHS men's health friendly?

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Inconsistencies in CCG guidance on prescribing for erectile dysfunction leave many out of step with current guidelines and recommendations, which the authors argue 'has made it virtually impossible to deliver evidence-based compassionate, personalised care'.

Tadalafil became available as a generic medication in 2017, removing the cost implications of prescribing it at regular doses. Recent studies demonstrate its efficacy for treating erectile dysfunction, yet current CCG guidance is inconsistent

Erectile dysfunction (ED) and testosterone deficiency (TD) are now acknowledged as independent cardiovascular (CV) risk factors. ED increases coronary heart disease (CHD) risk by 50%, even greater in men under 45 years of age, and TD increases the risk of developing type 2 diabetes mellitus (T2DM) 3–4-fold and CHD mortality by 40–50%.[1,2,3]

Repeated efforts to introduce screening and active intervention for ED and TD have been frustrated by a series of decisions taken by 135 different clinical commissioning groups (CCGs) in England, based on limited subjective assessment of evidence and with little specialist clinical input. Despite sildenafil being licensed in 1998, in 2020, there is still no formal NICE guidance on either ED or TD.[4]

A few historical events are relevant to how we have reached the current chaotic situation. In 1998, faced by the fear of overwhelming demand for newly licensed sildenafil (Viagra), the Department of Health (DoH) introduced a series of restrictions (HSC1988 and HSC1999), itemising a series of conditions that would qualify for NHS treatment, most notably T2DM but excluding cardiovascular disease (CVD), where the greatest benefit of intervention was likely to be seen.[4] Prescribing was restricted to one tablet per week, based on a health and lifestyle study from 1982 that suggested that this was appropriate for the UK population, when in reality the rate was twice per week, if the 40% plus who would have had ED were excluded.[5] More could be given according to 'clinical need', but CCGs later chose to ignore this concept along with the qualifying condition of 'severe distress'.[4]

In 2014, the patent on sildenafil ran out and the price fell from £5 to 15p per tablet and sildenafil was made available to all men without restriction of number of tablets, yet local CCG interpretation insisted on keeping the one tablet per week. *This effectively means that it is possible to treat a man with 1 tablet per week for a whole year for around the price of a single tablet in 1998.* In the same time the prescription charge in England has risen from less than £3 to almost £10.

In the 2013/2014 Quality and Outcomes Framework (QOF), GPs were paid specifically for reaching targets of recording ED rates in men with T2DM, which seemed a major breakthrough for early detection and intervention, only for NICE to remove the payments after only one year, giving 'simplification' as the sole reason.[6] In 2017, patents ran out for tadalafil and vardenafil, but these remain outside NHS regulations and must be funded privately, unless the man has T2DM or a series of rare qualifying conditions. This goes against all other trends within the NHS, where cheap generics have been made available to facilitate patient and physician choice.

In the following sections, we will analyse the evidence behind various published CCG and NHS guidance and contradictory conclusions that have restricted access to appropriate diagnosis and interventions.

Evidence search

An internet search using Google and based on 'CCG guidance on Erectile Dysfunction', identified published documents in 2018 and 2019 from 13 of the 191 CCGs in England, and these were scrutinised to identify common themes. Publications during and before 2017 were excluded on the basis that they were undertaken before the patent for tadalafil was removed, or the British Society for Sexual Medicine (BSSM) guidelines on ED were published.[4]

Guidance was classified according to the following criteria:

1. Was a flowchart of first- second- and third-line therapies provided?
2. Was lifestyle change advocated before medication?
3. Was 'over the counter' (OTC) therapy suggested first?
4. Was the NHS availability of sildenafil and Schedule 11 qualifying conditions explained?
5. Was stopping cycling advocated as an alternative therapy?
6. Was first prescribing the medication with lowest acquisition cost mentioned?
7. Was NHS restriction to 4 tablets per month mentioned?
8. Was daily therapy with tadalafil as salvage or rehabilitation excluded in all cases?
9. Was measuring testosterone level and addressing low levels discussed as a therapy for ED?

These were scrutinised to identify common themes.

Guidelines and advice

CCG Guidelines 2018–2019

All 13 documents (see Table 1)[7–19] mentioned the importance of lifestyle advice in conjunction with oral therapy, but three mentioned that lifestyle advice should always be tried before therapy, without suggesting duration or whether this applied to all cases.[7,10,12] Three documents mentioned cycling as a risk for ED,[8,9,12] with one mentioning stopping cycling prior to prescribing any medication but gave no information on for how long.[9] One document mentioned the importance of numbness and neurological signs, but none mentioned that oral therapy is highly likely to be effective in these cases.

Only two guidance documents[7,12] recommended first advising all patients (if willing and able) to purchase Viagra Connect 50mg from a pharmacy, without any mention of cardiovascular assessment, diabetes or discussion that generic sildenafil was available on NHS prescription. The wording from Cambridge and Peterborough CCG was particularly strong in suggesting OTC Viagra Connect as first line in all cases.

Only the Kernow CCG[19] specifically identified the names of contributors to the guideline. The remainder were anonymous. In the case of Kernow, this involved a consultant urologist and was the only one to mention ED was a CV risk factor equivalent to smoking (hazard ratio [HR] 1.46).

All 13 documents mentioned that the 'drug with the lowest acquisition cost – sildenafil 25mg' should be used first, and that this is the only drug provided at NHS expense. All other drugs are subject to the 1999 NHS qualifying conditions, which can be found in a summarised format in the BSSM guidelines.[4]

All 13 also mentioned that only four tablets of generic sildenafil per month should be prescribed, only one mentioned the 1999 'severe distress' qualification, but five CCGs provided different interpretations. One (Mid Essex)[11] instructed that Viagra Connect 50mg should be the 'top up source' if patients required more than one tablet per week, without pointing out that this dose was unlikely to be effective, and therefore a waste of £19.99 for patients who had previously required titration up to 100mg. One document (Rotherham)[13] mentioned that more than four could be prescribed at the discretion of the clinician. Another (Bristol, North Somerset and South Gloucestershire)[16] approved more than four tablets per month as long as it was stated in the notes, (East and North Hertfordshire and Herts Valleys)[17] stated that a request for more than four would require all the doses to be private, and Kernow[19] stated one to two tablets per week.

Twelve of the 13 documents recommended that eight tablets at maximal dose should be prescribed before classifying patients as 'non-responders'. Ten of 13 listed the Selected List Scheme (SLS) qualifying conditions but with the severe distress category removed.

Five documents did not mention the status of daily tadalafil.[9,10,14,15,19] Seven mentioned that tadalafil 5mg should not be prescribed and should be 'de-prescribed' in all circumstances, even if effective and if necessary, with referral to a specialist. Patients should be changed to on-demand therapy, even if this had previously proved ineffective and even if the patient was required to pay privately. Only Ipswich[18] allowed tadalafil as 'green' for post-radical prostatectomy or post-radiotherapy patients, if initiated by secondary care with review at nine months. Others[7,8,11,13,16] mentioned the lack of evidence to support daily use following radical prostatectomy, while one[17] mentioned that tadalafil 5mg daily should not be used *solely* for benign prostatic hyperplasia (BPH) but did not comment on whether use for combined BPH and ED would be appropriate. Eleven of 13 quoted a 'robust' PRESQIP analysis (2015) that showed no additional efficacy versus on-demand tadalafil.

Six of 13 documents stressed the importance of measuring testosterone levels, and two quoted a cut-off of 12nmol/L.[8,9] One suggested only measuring testosterone if libido was low.[14] Three mentioned referring for hypogonadism without providing any

CCG	Flow chart	Lifestyle before drugs	First OTC Viagra Connect	Schedule 11 explained	Stop cycling	Lowest acquisition cost	4 tablets per month	Daily tadalafil therapy	T level defined (nmol/l)
Wilts[7]	Y	Y	Y	Y	N	Y	Y	X	N
West Essex[8]	Y	N	N	N	Y[a]	Y[b]	Y	X	Y <12
Camden[9]	Y	N	N	Y	Y	Y	Y	N	Y <12
Sunderland[10]	Y	Y	N	Y	N	Y	Y	N	N
Mid Essex[11]	Y	N	N	Y	N	Y[c]	Y[d]	X must switch	N
Cambridge and Peterborough[12]	Y	Y	Y	Y	Y	Y	Y	X[e]	N
Rotherham[13]	Y	N	N	Y	N	Y[f]	Y[g]	X	Y[h]
Wirral[14]	Y	N	N	Y	N	Y	Y[i]	N	Y[j]
Thames Valley[15]	N	N	N	Y	N	Y[k]	Y	N	N
Bristol North Somerset and South Gloucestershire[16]	Y	N	N	Y	N	Y	Y[l]	X	Y (no level)
East and North Hertfordshire and Herts Valleys[17]	N	N	N	Y	N	Y	Y[m]	X	N
Ipswich and East Suffolk[18]	N	N	N	Y	N	Y	Y	Y[n]	N
Kernow (Cornwall)[19]	Y	N[o]	N	Y	N	Y	N (4–8 per month)	N	Y (no level)

Notes to the table: a. Stop cycling only if neurological symptoms such as tingling are present; b. Mentions efficacy in two out of three of patients with generic sildenafil; c. Mentions efficacy in 80% of patients with generic sildenafil; d. Suggests topping up with Viagra Connect OTC if more than one table per week is desired; e. Lowest acquisition cost of daily tadalafil listed as £5.66 per month; f. Ask for patient goals and expectations; g. GP may exercise clinical discretion and prescribe more than four tablets per month; h. Age-related testosterone levels quoted at <10nmol/L in patients less than 50 years; <9nmol/L in patients aged 50–75 years; <8nmol/L in patients aged above 75 years (no reference given); i. If more than four tablets per month are required, switch to private; j. Measure testosterone with 'loss of libido'; k. Alprostadil cream, vacuum device and psychosexual therapy not endorsed due to lack of efficacy; l. Any variation must be documented in notes; m. Four tablets per month for most men, but more if required; n. Daily tadalafil endorsed for prostate cancer rehabilitation if commenced in secondary care and reviewed at nine months; o. Stressed that ED is CV risk factor associated with HR of 1.46.

Table 1. Summary of advice provided by 13 Clinical Commissioning Group guidance statements between 2018–19 on the diagnosis and management of erectile dysfunction

values.[14,16,18] One (Rotherham)[13] mentioned a cut-off of <10nmol/L for men aged under 50 years, with a cut off of <9nmol/L for those aged 50–75 years, and <8nmol/L for men aged >75 years, but no reference was provided.

All 13 mentioned that second-line drugs such as intracavernosal, vacuum devices and intra-urethral drugs are subject to Schedule 11 guidance, but none mentioned whether these rules applied to psychosexual therapy or penile prosthesis. Thames Valley CCG[15] was alone in stating that there was insufficient evidence to support the use of topical alprostadil cream or psychosexual therapy, significantly reducing the options for patients in that region. No guidelines mentioned extracorporeal shockwave therapy.

Although NICE has never produced formal guidance on ED, a CKS was produced in 2017, but the recent 2019 revision[20] included multiple changes that were based largely on the 2018 BSSM and European Association of Urology (EAU) guidelines. These significant changes in relation to the nine classified areas are summarised in Table 2.

Discussion

Our results demonstrate considerable regional variation in advice given to GPs for ED treatment. This is likely to cause considerable confusion for patients who change address, and for secondary care providers who receive referrals from multiple CCGs. There is also considerable variation from the latest NICE CKS, which is based on the most recent BSSM and EAU guidelines.

In the documents investigated, there was a very good use of standard of care flowcharts based on expert guidelines, but a misinterpretation of lifestyle advice that should essentially be in addition to therapy and not as a substitute. There is a strong evidence base that intensive lifestyle intervention over a two-year period in men without CVD produces a clinically insignificant improvement in erectile function.[21] Only bariatric surgery or a loss of 15% body weight was associated with clinically significant changes. In men with T2DM, several studies have shown lifestyle change alone to be ineffective.[22] Therefore, the suggestion that lifestyle alone is likely to provide improvement in ED is inappropriate.

There was an over-emphasis on the impact of cycling on ED, and current expert opinion is that this is a minor problem that is only seen in conjunction with numbness associated with neurapraxia and is best managed with change to an appropriately designed saddle and regular PDE5 inhibitors that increase nitric oxide production by damaged nerves, aiding recovery.[23] Advice to stop cycling altogether for a long period is likely to negatively impact the health benefits, and is highly likely to be ignored by keen cyclists.

Once CCG (Cambridge and Peterborough)[12] suggested ALL men, irrespective of known or unknown comorbidities should be directed to pay £19.99 for four Viagra Connect tablets from a pharmacy if they are 'willing and able'. This local decision potentially undermines 25 years of research establishing ED as an independent CV risk factor that merits comprehensive investigation and management within primary care.[1–4] This was strongly endorsed by the CCG guidance from Kernow,[19] which was the only one that stated that it was consultant led.

Schedule 11 regulations were stated in all cases, but the BSSM guidelines clearly question the current relevance of the 1999 DoH guidance in 2020.[4] Sildenafil was taken out of Schedule 11 regulations in 2014 and a year's supply is now similar cost to a single Viagra tablet in 1998. Two other PDE5 inhibitors are now cheap and generic,[4] and even daily tadalafil 5mg has an acquisition price of only £5.66 per month. Surely the issue could now be managed by drug formularies in the same way as other therapy areas where only generics are allowed on formularies. The health economic argument for treating ED has been well established, even before the prices fell by 90% with the availability of generic products.[25] The great paradox of Schedule 11 regulations is that men who are unable to afford private medication charges are being increasingly referred to secondary care and can now opt for penile implants that are available at a cost of £8–10K at NHS expense.[4]

All CCGs endorse the principal of using the drug with the lowest acquisition cost, which is sildenafil 25mg, yet NICE CKS clearly states the importance of addressing the expectations of the patient to allow an

Search parameter	NICE CKS statement, August 2019
Flowchart	Yes
Lifestyle statement	Yes, in addition to therapy
OTC prescribing	Not mentioned
Schedule II	Yes
Cycling	Not mentioned
Lowest acquisition statement	Properties of each tablet should be explained to allow patient to make an informed choice. Inadequate dose and restriction of tablets is a major cause of treatment failure. Repeated failure is likely to cause considerable loss of confidence
4 tablets per month	Many couples find on-demand therapy totally unacceptable. Daily dosing may restore nocturnal erections, increasing the chance of spontaneous success. Only 8–12% respond to change to a second on-demand drug
Daily tadalafil statement	Up to 57% of men with an unsuccessful response to on-demand therapy will respond to daily tadalafil 5mg or even 10mg daily. Only 8–12% will achieve success with a second on-demand medication. Second-line therapies considerably more expensive and are often unpleasant to use
Testosterone measurement plus level	Up to 20% of men with erectile dysfunction will have a total testosterone below 12nmol/L and may benefit from a course of testosterone replacement therapy for up to six months

Table 2. Summary of the NICE Clinical Knowledge Summaries (CKS) for erectile dysfunction[20]

informed choice, recognising that many couples find on-demand therapy totally unacceptable. Analysis of clinical trial data shows there is not a single study in the literature involving sildenafil versus placebo restricted to once per week. Clinical trials involved access to unrestricted medication at maximal dose, though this still only produced response rates of 70% overall and 55% at best in T2DM.[4] Entry criteria were restricted to heterosexual couples in long-standing relationships currently attempting regular sexual activity. The results cannot be extrapolated to single, divorced or widowed for several years, gay or bisexual men or those seeking to father children.[4] For too long, this restriction, based on a lifestyle studies of the UK population from the 1970s has led to treatment failure, despair and relationship breakdown.[5] The suggested regimens of four tablets at the lowest dose, allowing for eight attempts with each dose escalating from 25mg to 50mg to 100mg, merely results in a vital loss of several months, multiple precious GP appointments followed by unnecessary secondary care referrals.[4]

Secondary care will therefore see increasing numbers of on-demand sildenafil failures. NICE CKS tells us that a second on-demand tablet will lead to success in 8–12% of cases, whereas daily tadalafil leads to a 57% success in patients who failed to respond adequately to sildenafil.[20] Faced with either a 57% chance in return of morning erections and the opportunity of frequent spontaneous sex compared with an 8–12% response based on further restrictions to one tablet per week there is only one choice for the informed patient, either by NHS or private. Unfortunately, the advice of 12 of 13 CCGs was to recommend a second or third on-demand drug with low chance of success. This clearly contradicts the NICE CKS evidence that restriction of tablets is a major cause of treatment failure and that patients and their partners should be involved in decisions. Seven CCGs (see Table 1) insisted that daily tadalafil must be stopped *even if proving effective*, a statement that undermines the basic ethical principles of clinical practice and potentially the human rights of the patient. Five were silent on this issue and only Ipswich and East Suffolk[18] endorsed daily tadalafil for prostate cancer patients if initiated in secondary care.

Unfortunately, the PrescQIPP review of 2015[26] only assessed studies of less than 12 weeks where tadalafil 5mg daily was compared with tadalafil 20mg with unrestricted medication,

with 2.3 tablets being taken per week, meaning effectively, that 35mg per week was being compared with 46.33mg.[4] Since then four meta-analyses and a long-term longitudinal study have confirmed the superior efficacy and patient and partner preference of 5mg daily versus on-demand therapy for men with ED with or without BPH.[27–32] The benefits are even more marked in terms of sexual encounter profile (SEP) data recorded at the time, rather than the International Index of Erectile Function (IIEF) score that involves men being asked to remember erections from six months earlier. These studies suggest that daily therapy is treating the pathological process of endothelial function rather than a symptom, ED.[27–31]

As ED is an acknowledged independent risk factor for CVD, there is now considerable evidence that PDE5 inhibitors reduce CV events and all-cause mortality in men with T2DM and previous myocardial infarction, and that benefits are more marked with frequent dosing.[33–35] This should come as no surprise as these drugs were initially developed to treat CVD. Only Kernow CCG[19] provided evidence for the importance of the association between ED and CVD and included a secondary care specialist on its panel. Kernow was also the only CCG to specifically list tadalafil as a licensed treatment for LUTS and/or BPH, which is associated with ED in over 50% of cases in men over 50 years old. Efficacy is equivalent to alpha blockers but with significantly greater patient satisfaction.[32]

It is disappointing that only six of 13 CCG guidelines mentioned measuring testosterone levels, and only three gave any indication of action levels – especially as NICE CKS states that 20% of men will have testosterone levels that require treatment.[20] A recent *BMJ* editorial reported that many men with ED and low testosterone are inappropriately diagnosed with depression and treated with SSRIs that cause long-standing persistent sexual dysfunction,[36] often requiring private therapy funded by the patient. NICE CKS endorses BSSM guidance[37] that testosterone therapy for up to six months is highly effective in such cases and frequently restores response to PDE5 inhibitors.

Conclusion

Our findings suggest that the current CCG guidelines need urgent review to bring them in line with current NICE CKS, BSSM and EAU guidelines. We have described several inconsistencies in advice between CCGs that have little evidence, and that much of the established evidence has been misinterpreted by local committees. We suggest that many CCGs and their predecessors have restricted access to life changing medical treatments for the last 20 years and, in the light of current evidence, this needs to be urgently addressed.

There is evidence of considerable regional variation in the treatments available for patients presenting with ED, which has been shown to have a significant impact on patients' quality of life. The recent NICE CKS evidence is a major step forward for primary care as it embraces findings from several expert guideline groups, but formal NICE guidance on ED and TD is still awaited. We would also suggest that the Schedule 11 ED guidance of 1999 is now irrelevant to clinical practice in 2020 and should be removed in light of generic ED therapies and the proven quality of life and CV benefits of treatment. For specialist clinicians involved in treating men with ED, the current outdated and conflicting guidance from CCGs has made it virtually impossible to deliver evidence-based, personalised care.

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