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Healthcare Reform in the United States; Facts, Fiction and Drama:Act II

Khalid J Qazi

Claiming historic triumph, that has defined his presidency ever since, President Barak Obama signed the \$ 1 trillion Patient Protection and Affordable Care Act (in short called as ACA) in a highly visible white house ceremony on Tuesday March 23, 2010 (using 20 different pens) thereby establishing health care as a 'right' of every American for the first time. It took all the legislative and political skills from him to get the bill passed through both houses of Congress as was suggested on these pages previously.¹

Soon after President Obama signed the landmark legislation, 26 States filed law suit contesting that the health care legislation, which earned the nickname of "Obamacare" from its opponents, was unconstitutional for several reasons. The legal challenge created significant uncertainty about the viability and future implementation of the legislation. There was also growing concern about the law's impact on the national debt that became, and continues to be, an extremely divisive issue between the Democrats and the Republicans in the US Congress.

The law suit finally, as expected, made its way to the Supreme Court of the United States. The Court was looking at the legislation from three angles. First, at the core of the legislation, was the requirement that nearly all Americans obtain health insurance by 2014 or face a financial penalty- a provision that came to be known as the 'individual mandate'. The penalty would be recycled into "health exchanges" providing alternate options to low income Americans and small businesses for purchase of health care. The 'individual mandate' was the backbone of the legislation that would cover millions of uninsured Americans, majority of whom would be healthy young individuals. And, if this 'individual mandate' were to be struck down by the Court (as was expected by many), then the second question would be what happens to the rest of the ACA as insurance industry was supporting the legislation since it would provide them with tens of millions of new healthy 'customers'. If such healthy individuals were left out, the pool would have mostly sicker individuals compromising the profitability, and perhaps the very viability, of the insurance industry. The third issue related to the mandate for the states to accept a large number of individuals into Medicaid program

that provides health care for the poor and those with income of up to 133 % of the federal poverty level.²

The Supreme Court, mercifully for President Obama, upheld virtually the entire legislation in its historic decision on June 28, 2012. The four 'liberal justices' (Justices Stephen Breyer, Ruth Ginsburg, Elena Kagan and Sonia Sotomayor) were joined by the conservative Chief Justice John Roberts in upholding the 'individual mandate'. In what many observers of the court called a surprising twist, the justices held that the mandate was not constitutional under the 'interstate commerce clause', as argued by the administration, but was constitutional under Congress' power of taxation. The other four dissenting conservative justices (Justices Samuel Alito, Anthony Kennedy, Antonin Scalia and Clarence Thomas) held that the Congress had exceeded its authority on several levels.

The reaction to the ruling was prompt and mixed. Dr. Jeremy A. Lazarus, President American Medical Association said "The AMA has long supported health insurance coverage for all, and we are pleased that this decision means millions of Americans can look forward to the coverage they need to get healthy and stay healthy". The President and CEO of American Hospital Association, Mr Rich Umbdenstock, said "The decision means that hospitals now have much-needed clarity to continue on their path toward transformation". Perhaps the President of the American College of Physicians stated it best "We hope that a day will come when the debate will no longer be polarized between repeal on one hand, or keeping the law exactly as it is on the other, but on preserving all of the good things that it does while making needed improvements."

The President of the U.S. Chamber of Commerce, Thomas J. Donohue, lamented that "While we respect the court's decision, today's Supreme Court ruling does not change the reality that the health care law is fundamentally flawed. It will cost many Americans their employer-based health insurance, undermine job creation and raise health care costs for all." And in a scathing statement, the President of National Federation of Independent Business, Dan Danner, echoing the sentiments of a growing number of small businesses said "Under [the ACA], small-business owners are going to face an onslaught of taxes and mandates, resulting in job loss and closed businesses. We

will continue to fight for the repeal of [the ACA] in the halls of Congress; only with [the ACA's] full repeal will Congress have the ability to go back to the drawing board to craft real reform that makes reducing costs a No. 1 priority.”³

This line of argument, apart from bringing some uncertainty, provided politicians fodder as they move closer to the Presidential elections. And as expected, the Republicans (who control the House of Representatives) passed legislation repealing the law but the bill died in the US Senate (controlled by Democrats). And the Republican Presidential candidate, Gov. Mitt Romney, framed the decision as a political call to arms. “What the Court did not do on its last day in session, I will do on my first day if elected President of the United States. And that is I will act to repeal Obamacare.” While both President Obama and Gov. Romney agree that Medicare costs have to be reined in but there is fundamental difference in their approach to cost cutting. President Obama’s plan relies on a powerful board to reduce payments to service providers and gradually changing how hospital and doctors are paid in order to eliminate fee for service and establish pay for performance (pay for the quality, not quantity). Gov. Romney would limit the amount future retirees would receive from the federal government to approximately \$ 7000 (also called as Voucher System) and relying on the private industry to find an efficient solution.

It is clear that Gov. Romney, who previously implemented ‘Obamacare’ type of legislation as the governor of Massachusetts, flipped his position to appease extreme right wing of the Republican Party. As usual politics trumps policy. This drama continues to play out as we get closer to the election on November 6, 2012.

As identified by an independent nonpartisan educational institute based in Washington, The Centre for American Progress (CAP), some of the popular provisions of the law are⁴:

- The law provides for young adults to stay on their parents’ insurance to age 26 enabling 2.5 million young Americans to enrol on their parents policies (73 % of young adults now have coverage as a result of this provision);
- For seniors living on fixed income (Medicare patient population), one of the immediate benefits of the ACA was the closure of prescription drug coverage gap (known as the ‘donut hole’) saving 4 million seniors about \$ 2 billion on prescription drugs or approximately \$604 per person, in 2011 alone;
- The law provides \$11 billion to support and expand community health centres nationwide. More than 350 new community health centres were established in 2011 serving 50 million Americans in medically underserved areas;
- Starting in 2014, the law prohibits health insurance carriers from excluding and/or denying coverage or charging higher premiums and limiting benefits to those with pre-existing medical conditions (as happens currently in too many cases);

- 50,000 Americans have already enrolled in the Pre-existing Condition Insurance Plan (PCIP) that ensures medical services including prescription drugs for those with pre-existing conditions as soon as possible ;
- Provision of \$200 million to expand school-based health centres for primary care, dental care, behavioural health services and substance abuse counselling;
- In 2011 alone, 85 million Americans benefitted from preventive services included in the legislation. Many more will benefit since a major provision of the preventive services for women took effect in August 2012;

However, several components of the legislation remain unclear and their impact rather unknown. As an example the Obama administration fought hard for formation of the Independent Payment Advisory Board (IPAB) to address the inordinate influence of stakeholders in Congressional decisions over Medicare. This group of 15 nonpartisan experts is responsible for developing payment and related Medicare policy changes to assure that Medicare spending does not exceed budget targets tied to economic growth. Although now the law, the IPAB may never be formed because the Senate is unlikely to find 60 votes required to confirm IPAB members (unless the election brings unforeseen changes in the makeup of the Senate). Politics may again triumph policy. The payment approaches that need to evolve from “volume” to “value,” remain vexing. The Centre for Medicare & Medicaid Innovation charged with developing the pilot programs that may result in a reformed delivery system, have no pilots that focus on developing alternative models to reimburse physicians services.^{5,6}

And the “invisible problem” of physician shortage! While there is growing bipartisan appreciation that the primary care workforce is insufficient to handle increasing demand for primary care services, the problem has not been fully addressed. The Association of American Medical Colleges estimates that in 2015 the country will have 62,900 fewer doctors than needed and those numbers will more than double by 2025.^{7,8}

In coming months the States may become the battleground for implementing the “health exchanges”. By 2014 States are required to establish American Health Benefits exchanges and small business health operations program (SHOP) exchanges. These exchanges called in short, “health exchanges”, are basically subsidized market places with tax credits for consumers to shop for their health insurance at very competitive rates. Individuals who will not be eligible for Medicaid and with income of up to 400% of the Federal poverty level will have access to these health exchanges to purchase insurance. Such subsidies and tax credits will also be available to businesses with less than 100 employees.⁹

It is also becoming apparent that the financial burden of the legislation will be significantly higher than initially estimated. For example the non-partisan Congressional Budget Office (CBO) estimates that 80 % of Americans who will face penalty

for lack of health insurance under the ‘individual mandate’ would be those with yearly income of \$ 55, 250 (for individuals) and \$ 115, 250 (for couples). This is in contrast to the statements of President Obama who continues to pledge that he will not raise taxes on individuals making less than \$ 200,000 and couples making less than \$ 250, 000. And the Republican side of the Senate Budget Committee estimates that Obamacare will cost \$2.6 trillion dollars in its first real decade since the bill does not fully go into effect until 2014.¹⁰

Fortunately for President Obama, the prestigious Institute of Medicine released a report, last month on September 6, confirming what has been suggested by him and others, that the US health care system wastes almost 30 % (\$750 Billion) each year on unnecessary procedures, fraud and waste. Therefore, the administration has redoubled its efforts to check the waste and fraud in order to pay for the cost of ACA. However, the real battle will begin as soon as the Congress reconvenes in January 2013. They are immediately faced with dealing with “Sequestration”. Originally a legal term referring to the act of valuable property being locked away for safe keeping by an agent of the court, the term has been adapted by Congress in 1985 for fiscal discipline. Under this rule, an amount of money equal to the difference between the cap set in the Budget Resolution and the amount actually appropriated is “sequestered” by the department of Treasury and not handed over to the departments it may have been appropriated originally by the Congress. The balanced budget act of 2011 established a Congressional task force (called ‘Super Committee’) that was charged to make recommendations to cut the US Budget deficit by \$ 1.5 trillion by November 23, 2011. Failure to do so would automatically trigger “Sequestration”. On November 21, 2011, the committee issued a statement that it had failed to reach agreement. This failure is viewed by most as a triumph of political ideology over genuine leadership. But the prospect of ‘sequestration’ has come to be seen so catastrophic that key members of Congress and the President are expected to abandon brinkmanship and come to an agreement in early 2012.

So, as the drama and the debate continue vigorously in the days leading up to the November 6 elections, it is clear that “Obamacare” will continue to divide the US congress and the country. Irrespective of the party that will control the Congress and who becomes the next President of the US, “Obamacare” is here to stay. And, no matter how hard the Republican Party may try, they will face a monumental task in reversing the course of the history. There will be bickering, name calling,

finger pointing and horse trading. But, the warring factions will realize that the escalating costs and complexities of the health care system demand that the legislators and the President come together to find real solutions to keep the American health care system as the best in the world. The real challenges will remain the same no matter who is elected as President: to stem the unsustainable tide of national health expenditure as percentage of the gross national product (rising from 7.2 % in 1970 to over 17 % in 2010), rapidly increasing number of Americans without health insurance (approaching almost 50 million), exploding national debt and, more immediately, the looming threats from sequestration.

Competing Interests

None

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3 years on: Examiners' and candidates' views on the CASC (Clinical Assessment of Skills and Competencies)

Rajkumar Kamatchi, Saugata Bandyopadhyay, Ashok Kumar Jainer, Bettahahalasoor Somashekar, Marek Marzanski and Steven Marwaha

ABSTRACT

Aim and method: The Clinical Assessment of Skills and Competencies (CASC), introduced in June 2008 is the new and only clinical examination in obtaining membership of Royal College of Psychiatrists. Although there is evidence of strong validity and reliability for OSCE (Objective Structured Clinical Examination) - type examinations, the acceptability, validity and reliability of the CASC is open to challenge. We conducted a national online survey of candidates and examiners to obtain their views and aimed to evaluate whether the CASC fulfils its purpose.

Results: The survey showed that 48% of the candidates (n=110) and 59% the examiners (n=22) agreed that the CASC examines the required competencies to progress to higher training. However only 15% of the candidates and 18% of the examiners accepted that CASC examines all the advanced psychiatric skills compared to the previous Part 2 clinical examination. Nevertheless, only a third of the candidates and examiners considered replacing the CASC with traditional long case as the best way forward.

Implications: Although CASC scenarios may reflect real-life situations and its content covers most skills in piecemeal, it lacks the holistic ethos underpinning the bio-psychosocial approach unique to psychiatry. The findings of the survey suggest that the current examination method requires further systematic evaluation.

Post-graduate medical education in the United Kingdom has seen numerous dramatic changes in the last decade, with the introduction of structured training programmes and changes in assessment of skills driven by Modernising Medical Careers.¹ Overall these new developments emphasise a competency based curriculum and assessments. Alongside and contingent on these wider changes in medical education, psychiatric trainees have faced major transformations in their membership (MRCPsych) examinations.

The MRCPsych examination was first introduced in 1972, a year after the Royal College of Psychiatrists was founded. There have been various modifications in its structure since its inception but a radical change occurred in the last decade with the introduction of an OSCE in 2003 and the CASC, a modified OSCE in June 2008. The CASC is considered as a high-stakes examination as it is now the only clinical and final examination towards obtaining the membership of the College. The MRCPsych qualification is considered as an indicator of achieving professional competence in the clinical practice of psychiatry and has the main aim of setting a standard that determines whether trainees are suitable to progress to higher specialist training.² In his commentary to Wallace et al³, Professor Oyebode describes the aims, advantages and disadvantages of the various assessment methods used in the MRCPsych examination and conclude that the precise assessment of clinical competence is essential.⁴

Traditionally, assessment of clinical skills involved a long case examination since it was introduced in clinical graduating examination by Professor Sir George Paget at Cambridge, UK in 1842. This has been followed by most of the medical institutions worldwide and remained as the clinical component of the MRCPsych examination until 2003. There are some shortcomings with this assessment method and the outcome can be influenced by several factors such as varying difficulty of the cases, co-operation of the real patient and examiner-related factors. The reliability of assessment of clinical competency with a single long case is low and it is necessary for the candidate to interview at least ten long cases to attain the reliability required for a high stakes examination like MRCPsych.⁵ A fair, reliable and valid examination is necessary to overcome these difficulties. The OSCEs proved to be one of the answers to these difficulties.

One important aspect of assessing the validity and acceptability of assessment methods is asking the opinions of examiners and candidates about their experiences and views about the examination once it has been rolled out. As far as the authors are aware there has been one previous published survey of CASC candidates' views on this method of examination and this was based at a revision course. Whelan et al⁶ showed that approximately 70% of the candidates did not agree with the statement "there is no longer a need to use real patients in post-graduate clinical psychiatry exams". In addition, only 50% of the candidates preferred the CASC compared to previous long case and the other 50% remained undecided. This raises doubts

about the acceptability of the CASC format and merits further exploration.

Method

We conducted a national on-line survey asking both candidates and examiners about their views on the CASC examination.

Questionnaire development

Two questionnaires (one each for examiners and candidates) based on previously available evidence on this exam format^{6,7,8} were developed following discussions among the authors.

The final version of the questionnaire for both groups had the same seven questions with a five point Likert scale. It included questions on whether the exam effectively assessed the competency needed for real life practice, whether there was over testing of communication skills, whether feedback was adequate, respondents' views on validity and reliability of the method and finally whether the clinical examination should revert to the previous style of long case and viva.

Sampling procedure

The examiners and the candidates who have already appeared in the CASC examination were invited to complete the online survey. The links to the questionnaires were distributed via the Schools of Psychiatry in thirteen deaneries in the United Kingdom (including Wales, Northern Ireland and Scotland). We approached 400 candidates and 100 examiners from different deaneries making sure the wide geographical distribution. The sample size was chosen based on the data that around 500 candidates appear in CASC exam each time and there are approximately 431 examiners on CASC board (personal contact with the College). Participants were assured that their responses were confidential. The survey was open from mid-March to mid-April 2011. Reminders were sent half way through the survey period.

Results

A total of 110 candidates and 22 examiners completed the survey. The response rate was better for candidates (27.5%) compared to the examiners (22%). Albeit the low response rate, the responses showed good geographical spread. Responses were received from most of the deaneries (87%). The London, East and West Midlands deaneries showed higher response rate (14% each) while Scotland, Severn and North Western deaneries showed least response rate (2% each).

Among the 110 candidates, 52% were males and 48% were females and among the examiners, 73% were males and 27% were females. 55% of the examiners were involved in the previous Part 2 clinical exam while only 7% of the candidates had the experience of previous Part 2 clinical exam. The results are summarised in Tables 1 and 2.

Clinical competencies and skills

59% of the examiners and 48% of the candidates have accepted that CASC examines the required competencies to progress to higher training. Strikingly only 18% of the examiners and 15% of the candidates agreed that CASC allows the assessment of all the skills and competencies necessary for the higher trainees in comparison to the previous Part 2 clinical exam.

Content of the CASC

Majority of the examiners (77%) and nearly half of the candidates (48%) agreed that CASC scenarios reflect real life situations faced by clinicians in normal practice. However 60% of the candidates and 48% of the examiners felt that CASC excessively emphasizes communication and interview skills.

Feedback - "areas of concerns"

More than half of the candidates (60%) and half of the examiners (50%) felt that the feedback indicating "areas of concerns", for the failed candidates was not helpful to improve their preparations before the next attempt.

Validity and reliability of the CASC as a clinical exam

Just over one fourth of the candidates (28%) and less than half of examiners (46%) considered CASC as a valid and reliable method of clinical examination. However, only 36% of the candidates and 32% of the examiners supported replacing CASC with a traditional clinical exam (a long case and a viva). Broadly comparable numbers (39% of the candidates and 27% of the examiners) disagreed with the statement that the CASC should be replaced by the previous examination style.

Discussion

To our knowledge this is the first study of candidate and examiner views since the introduction of the CASC. Its predecessor OSCEs has a good reliability and validity in assessing medical students⁸ and it has become a standard assessment method in undergraduate examinations. Whilst OSCEs have been held to be reliable and valid in a number of assessment scenarios,⁸ there have been doubts about their ability to assess advanced psychiatric skills,⁹ which was one of the main reasons to retain the long case in MRCPsych Part 2 clinical exam.² Over the years, most of the Royal Colleges introduced OSCEs into their membership examinations and used simulated patients in some scenarios. However CASC is the first examination with only simulated patients in a combination of paired and unpaired stations. So far there has been no published literature evaluating this method systematically.

Table 1. Candidates' views (n= 110)

Survey questions	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
CASC examines the required competencies to progress to higher training	10%	38%	7%	26%	19%
CASC examines all skills and competencies compared to previous Part 2 clinical exam	4%	11%	46%	21%	18%
CASC scenarios reflects the real life situations faced in clinical practice	12%	36%	13%	22%	17%
CASC gives more emphasis on testing communication and interviewing skills than overall competencies	29%	31%	14%	19%	7%
CASC is more valid and reliable as a clinical exam	9%	19%	29%	20%	23%
Feedback system 'areas of concern' are helpful to the unsuccessful candidates	1%	11%	28%	26%	34%
CASC needs to be replaced by traditional style of exam – a long case and a viva	14%	22%	25%	24%	15%

Table 2. Examiners' views (n= 22)

Survey questions	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
CASC examines the required competencies to progress to higher training	14%	45%	14%	18%	9%
CASC examines all skills and competencies compared to previous Part 2 clinical exam	4%	14%	23%	45%	14%
CASC scenarios reflects the real life situations faced in clinical practice	14%	63%	5%	9%	9%
CASC gives more emphasis on testing communication and interviewing skills than overall competencies	22%	26%	17%	22%	13%
CASC is more valid and reliable as a clinical exam	9%	37%	27%	9%	18%
Feedback system 'areas of concern' are helpful to the unsuccessful candidates	0%	36%	14%	27%	23%
CASC needs to be replaced by traditional style of exam – a long case and a viva	18%	14%	41%	9%	18%

In a recent debate paper¹⁰ it has been argued that CASC may have significant problems related to its authenticity, validity and acceptability. The findings of our survey reflect similar doubts about the reliability and validity of the CASC exam amongst both the candidates and examiners. The content validity of CASC has been demonstrated by the College Blueprint¹¹ and the face validity appears to be good. However, as far as we are aware, the concurrent and predictive validity testing data have not been published. Although the global marking system appears to have better concurrent validity than other checklists, it gives the examiners the similar flexibility as the long case in making judgements which may affect CASC transparency and fairness. This may indicate that this new and promising examination method requires further systematic evaluations and modifications before its user's fully accept it.

According to the results of our study the content of the CASC exam satisfies its purpose of assessing the candidates' competencies to progress to the higher professional training. However many of the respondents felt that it lacked the completeness of previous traditional clinical examination, which collate skills. Although there were some differences between the

candidates and the examiners on how they perceived the CASC exam, most of the respondents agreed that CASC laid more emphasis on communication and interviewing skills rather than overall assessment of the candidate's competency.

Harden et al,¹² in their paper on OSCEs, criticised the compartmentalisation of knowledge and discouraging candidates from a broader thinking during the clinical examinations. They also suggested using a long case and/or workplace based assessments rather than relying on OSCEs only in assessing trainees. Benning & Broadhurst¹³ expressed similar concerns on the loss of long case in MRCPsych examination. Our findings support the arguments that CASC assesses competencies in a piecemeal fashion rather than being reflective of the demands on senior doctors in real practice which often involve deciding what is and is not important depending on context.

The OSLER¹⁴ (Objective Structured Long Examination Record) method might overcome the shortcomings and improve the objectivity and transparency of long case. In this method, two examiners assess the candidate and grade their skills individually in a ten item objective record. Later they

decide together the appropriate grade for each item and agree an overall grade. The ten items include four on history, three on examination and another three covering investigations, management and clinical acumen. The OSLER method is also practical as no extra assessment time is required and it can be used for both norm referenced & criterion referenced exams. The case difficulty can be determined by the examiners and all candidates are assessed for identical items. Thus this method assesses the candidate's overall clinical competency and eliminates the subjectivity associated with the long case.

Another alternative might be using a combination of assessment methods as suggested by Harden.¹² An 8-10 stations OSCE can be combined with a long case assessment using OSLER method. The OSCE stations might include patient management scenarios along with interview and communication skills scenarios. The final score determining the result could also include marks from work place based assessments as they provide a clear indication of the candidate's skills and competence in real life situation.

It is also evident from our findings that both candidates and examiners are largely unsatisfied with the extent and usefulness of feedback that is provided to unsuccessful candidates. The feedback system have been criticised for its inability to clarify the specific areas or skills which need to be improved by the unsuccessful candidates. The recent "MRCPsych Cumulative Results Report"¹⁵ states that the pass rate of the candidates declines after the first attempt. Perhaps this could be improved if failed candidates receive more detailed feedback about their performance.

There are a number of limitations to this study. The response rate was low but it was broadly in the range of other online surveys¹⁶ and there was representation from most of the deaneries in the United Kingdom. There could be a number of reasons for low response rate. As far as we are aware few deaneries were not willing to distribute the questionnaire through their School of Psychiatry and we had to contact the individual trusts in the area to distribute the survey. The poor response rate from the examiners could be because of their low interests in participating and lack of time. Also older examiners and those with more experience of CASC may have had particular views which might have had an influence on the responses. But when this was examined further, there were no major differences between respondents who had the experience of previous Part 2 examinations from those who had not. In addition one of the survey questions consisted of two parts (views on validity and reliability) which could have been difficult to answer accurately.

The findings of this preliminary study raise some doubts on acceptability of the CASC by both candidates and examiners. There might be a possibility of subjective bias in the responders' views, perhaps influenced by other ongoing and controversial changes in the NHS, including the role of GMC and the

College in the post-graduate medical education. However on the other hand it might be a signal that it is worthwhile to reconsider the implications of the CASC on education and training and to evaluate systematically this assessment method further.

Competing Interests

None declared

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Postural Orthostatic Tachycardia Syndrome (POTS): Evaluation and Management

Ronald Conner, Mujeeb Sheikh and Blair Grubb

Abbreviations

JHS - Joint hypermobility syndrome, POTS - Postural Orthostatic Tachycardia Syndrome, SSRI - serotonin reuptake inhibitor, SNRI - norepinephrine reuptake inhibitor, EPO - erythropoietin

Case Presentation

A 29 year-old woman had been well until 7 months previously when, after a viral syndrome, she developed palpitations, fatigue, and frequent episodes of light headedness and near syncope. On further questioning she notes exercise intolerance and dyspnea on exertion. She has stopped working as cashier. Her mother thinks she is having panic attacks and needs “something to calm her nerves.” ECG, echocardiogram, and endocrine evaluation are all normal. On physical examination, she displayed a postural heart rate increase of 35 beats per minute on standing, along with a 15mmHg fall in diastolic blood pressure.

Introduction

Disorders of the autonomic nervous system present unique challenges to the practicing clinician. These syndromes have a significant impact on quality of life, offer subtle diagnostic clues, and have a propensity to mimic other disease processes. For these reasons clinicians should have basic familiarity with the differentiating features of autonomic disorders. While much investigation has focused on Neurocardiogenic syncope, a distinct subgroup has emerged characterized by postural tachycardia and exercise intolerance. Postural orthostatic tachycardia syndrome (POTS) is the final common pathway of a heterogeneous group of underlying disorders that display similar clinical characteristics.¹

The constellation of symptoms associated with POTS reflects underlying dysautonomia including palpitations, exercise intolerance, fatigue, lightheadedness, tremor, headache, nausea, near syncope, and syncope. Foremost amongst these is orthostatic intolerance. Besides being limited in the functional activities of daily living, increased sleep disturbances including excess daytime sleepiness, fatigue are also common and have been associated poor health-related quality of life.² We aim to

discuss the clinical presentation, classification, evaluation and management of POTS.

Diagnosis

The current diagnostic criteria for POTS is the presence of orthostatic intolerance symptoms associated with a sustained heart rate increase of 30 beat per minute (bpm) or absolute rate exceeding 120 bpm within the first 10 minutes of standing or upright tilt in the absence of other chronic debilitating disorders, prolonged bed rest, or medications that impair vascular or autonomic tone.³ Most patients will have orthostatic symptoms in the absence of orthostatic hypotension (a fall in BP >20/10 mmHg). A grading system for POTS has been developed (Table 1). This system focuses on the functional severity of orthostatic intolerance in a way similar to the NYHA heart classification.

The physical exam should be methodical and directed. Supine, sitting, and immediate standing heart rate and blood pressure should be recorded. Orthostatic tachycardia and acrocyanosis of the lower extremities may be the only physical signs in these patients. Standing and supine blood pressure measurements and baseline electrocardiogram are generally recommended. In patients with physical examination or clinical history suggestive of cardiovascular abnormalities, other diagnostic test including echocardiogram, stress test or coronary angiography may be indicated before a tilt test. In addition, other possible clinical disorders with similar clinical manifestations must be kept in mind and ruled out. Upright tilt test remains the diagnostic test of choice for POTS and other autonomic disorders. Implantable loop recorders, electrophysiological tests and Holter monitoring are not helpful in the evaluation of these disorders. Supine and upright serum catecholamine levels should be obtained if hyperadrenergic type is suspected. In the presence of gastrointestinal symptoms bowel motility studies

may reflect the degree of involvement and help to tailor therapy.⁴

Table 1 : The Grading of Orthostatic Intolerance*
Grade 0 Normal orthostatic tolerance
Grade I Orthostatic symptoms are infrequent or occur only under conditions of increased orthostatic stress Subject is able to stand >15 minutes on most occasions Subject typically has unrestricted activities of daily living
Grade II Orthostatic symptoms are frequent, developing at least once a week Orthostatic symptoms commonly develop with orthostatic stress Subject is able to stand >5 minutes on most occasions Some limitation in activities of daily living is typical
Grade III Orthostatic symptoms develop on most occasions and are regularly unmasked by orthostatic stresses Subject is able to stand for >1 minute on most occasions Patient is seriously incapacitated, being bed or wheelchair bound because of orthostatic intolerance Syncope / presyncope is common if patient attempts to stand
*Symptoms may vary with time and state of hydration and circumstances. Orthostatic stresses include prolonged standing, a meal, exertion, and head stress.

Classification and Clinical Features

POTS is a heterogeneous group of disorders resulting in a common clinical scenario. This syndrome is classified as being either primary or secondary. Primary POTS is idiopathic and not associated with other disease processes. Secondary POTS occurs in association with a known disease or disorder. Subtype classification affects management and is therefore essential.^{1,4} (Figure 1)

Partial dysautonomic (PD) POTS (also referred to as Neuropathic POTS) is the predominant form.^{1, 2} This is a mild peripheral autonomic neuropathy, characterized by inadequate peripheral vasculature constriction in the face of orthostatic challenge. Female predominance is seen with 5:1 female to male ratio. Presentation is commonly abrupt onset of symptoms after a febrile viral illness, pregnancy, immunization, sepsis, surgery, or trauma. The etiology of PD type POTS is postulated to be an autoimmune molecular antigen mimicry type pathogenesis. Serum autoantibodies to peripheral autonomic ganglion alpha-3 acetylcholine receptors may be positive in 10-15% of the cases. Anhidrosis of lower extremities is seen in more than 50% of these patients at quantitative sudomotor axon reflex testing. Dependent blood pooling when upright is greater than normal and heart rate and contractility increase as normal compensatory physiologic mechanisms to maintain cerebral perfusion. This autoregulatory response may initially be fully compensatory; however, peripheral venous pooling may increase with time and exceed this compensatory effect. Patients with PD type POTS become dependent on the

skeletal muscle pump to augment their autoregulatory physiology. Ultimately, venous blood pooling increases beyond the body's total ability to compensate and adequate blood pressure maintenance fails.

“Developmental” partial dysautonomic POTS is an adolescent subtype.⁶ The mean age of onset is 14 years. The clinical scenario is that of orthostatic intolerance following a period of very rapid growth. Symptoms are progressive and peak at a mean age of 16 years. Orthostatic intolerance may be severe, including severe headaches, and can be functionally disabling. Following their peak symptoms will slowly improve and resolve into young adulthood (19-24 years). Roughly 80% of patients with developmental PD POTS will experience complete resolution of symptoms. The etiology of this subtype is unclear and appears to be a transient period of autonomic imbalance occurring in rapidly growing adolescents.

Hyperadrenergic POTS is less common than the PD type.⁷ This form is characterized by a gradual onset with slowly progressive symptoms. Patients report experiencing tremor, anxiety, and cold clammy extremities with upright posture.⁷ Many patients note increased urine output when upright. True migraine headaches may be seen in over half of patients.⁷ Gastrointestinal symptoms in the form of recurrent diarrhea were seen in 30% of the patients. In contrast to PD type of POTS, the hyperadrenergic form demonstrates elevated serum catecholamine levels with serum norepinephrine levels >600ng/ml. This may be a familial syndrome in some instances determined by a careful history. The etiology of hyperadrenergic POTS is felt to be genetic with a single point mutation resulting in a dysfunctional norepinephrine reuptake transporter protein present in the intrasynaptic cleft. The result is excessive norepinephrine serum spillover with sympathetic stimulation resulting in a relative hyperadrenergic state appearing similar to pheochromocytoma.⁸

A connective tissue disorder has been an increasingly recognized etiology of secondary POTS.⁹ Joint hypermobility syndrome (JHS) is an inherited condition characterized by joint hypermobility, connective tissue fragility, and soft velvety skin with variable hyperextensibility. The condition is associated with ecchymotic predisposition, premature varicose veins, diffuse muscle and joint pain, and orthostatic acrocyanosis. The etiology of POTS in JHS patients is thought to be due to abnormal vascular (venous) elastic connective tissue. During orthostatic stress and increased hydrostatic pressure these patients exhibit increased vessel distensibility and orthostatic intolerance. Excessive peripheral venous pooling and compensatory tachycardia follows. Up to 70% of JHS patients suffer from some degree of orthostatic intolerance. It is observed that adolescent PD POTS patients have features similar to JHS patients and further studies may determine the significance of this potential relationship.¹⁰

Secondary POTS refers to a group of conditions which result in peripheral autonomic denervation with sparing of cardiac innervation. Most commonly, secondary POTS is associated with diabetes mellitus. Less commonly, this form may occur with heavy metal intoxication, multiple sclerosis, parkinsonism and chemotherapy, especially vinca alkaloids.^{11,12}

Severe autonomic nervous system disorders may present as POTS. These may include pure autonomic failure or multiple system atrophy. Paraneoplastic syndrome associated with adenocarcinoma of the lung, breast, ovary, or pancreas may also present as POTS. These tumors produce auto-antibodies targeting the acetylcholine receptors in the autonomic ganglia in a manner similar to post-viral syndromes.

Evaluation and Management

Treatment is generally individualized to each patient. Confounding pharmacology should be identified and stopped if possible (Table 2). The presence of secondary POTS should be considered. Underlying diagnoses causing or augmenting POTS should be identified and treated appropriately. Deconditioning is frequent seen in POTS patient and a deliberate aerobic reconditioning program should be a component of the treatment plan.¹³ This is encouraged to begin promptly working up to a goal of 20-30 minutes of activity at least 3 times a week. Resistance training of the lower extremities is helpful to increase the efficacy of the skeletal muscle pump. Salt and water ingestion are the most common employed non-pharmacological therapeutic intervention for POTS. Although, the intravenous saline infusion has been associated with reduction in standing tachycardia, the effect on this intervention on the symptom reduction remains unknown¹⁴. In general, since low blood volume may exacerbate symptoms patients are encouraged to have liberal salt and water intake. Excluding hyperadrenergic POTS, daily fluid and sodium intake should be greater than 2 liters and 3-5 grams.

Angiotensin-converting enzyme inhibitors	Opiates
Alpha receptor blockers	Diuretics
Calcium channel blockers	Hydralazine
Beta blockers	Ganglionic-blocking agents
Phenothiazines	Nitrates
Tricyclic antidepressants	Sildenafil citrate
Bromocriptine	Monoamine oxidase (MAO) inhibitors
Ethanol	

The goal of pharmacotherapy in the treatment of POTS is to ameliorate the symptoms of POTS and thus maintain the functional capacity. Currently no drug is US FDA approved for the treatment of POTS. All pharmacology is inherently off-label. (Table 3).

Majority of the evidence for the use of different pharmacological agents in the management of POTS is based on some small randomised, observational and retrospective single center studies. In clinical practice most patients are treated with a single agent and second medication from different class with a different mechanism of action is added in case of treatment failure. Resistant cases are often treated with polypharmacy.

Fludrocortisone, a potent mineralocorticoid resulting in sodium retention, augmented fluid volume, and sensitized peripheral alpha adrenergic receptors. The effects are more pronounced in the younger population. Starting dose is 0.1-0.2 mg daily with a maximum dose of 0.4 mg. Common side effects include electrolyte imbalance and hypertension. In a study of 11 female POTS patients, fludrocortisone alone or in combination with bisoprolol was associated with improvement in symptoms¹⁵. Midodrine is an alpha -1 adrenoceptor agonist and causes both arterial and venous vasoconstriction. It is commonly used as add on therapy and with starting dose at 5 mg orally three times a day. In our clinical experience we advise patients to take their first dose of midodrine 15 minutes prior to getting out of bed. An additional 5mg dose can be used for breakthrough symptoms. Midodrine is usually well tolerated with the most common complaints being nausea, "goose bumps," and scalp pruritus. In a small study of 6 patients with POTS acute combination therapy of midodrine (10mg) with octreotide (0.9mcg/kg) was significantly associated with reduction in upright tachycardia and improved standing time. In another study of 53 children with POTS, midodrine was significantly associated with both higher clinical cure rate and reduced recurrence rate as compared to children treated with metoprolol or conventional therapy.

Patients may continue to be symptomatic despite dual-therapy as outlined above. In this population we add a serotonin reuptake inhibitor (SSRI) or norepinephrine reuptake inhibitor (SNRI). SSRI therapy has been found to be helpful in the prevention of neurocardiogenic syncope. However, SNRI therapy is more useful in the treatment of POTS. Usually, we use bupropion XL beginning with 150 mg orally daily titratable to 300 mg daily if necessary.

The most effective SSRI therapies combine serotonin and norepinephrine reuptake inhibition (venlafaxine and duloxetine). The agents are usually well tolerated with the most common side effects being gastrointestinal upset, tremor, sleep disturbance, and less commonly agitation and sexual dysfunction. Bupropion and SSRI therapy can be combined to achieve a similar effect.

Pyridostigmine is an acetylcholinesterase inhibitor that facilitates sympathetic and parasympathetic ganglionic neural transmission. In our single center experience of 203 patients of POTS treated with pyridostigmine; improved symptoms of orthostatic intolerance were seen in 88 of 203 (43%) of total

Figure 1. Subtypes of postural orthostatic tachycardia syndrome

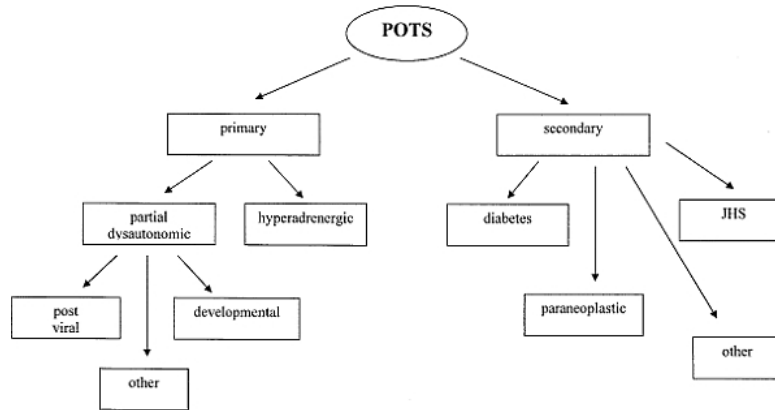


Table 3: Therapeutic Options in POTS

Treatment	Application	Form Effective in	Problems
Reconditioning	Aerobic exercise 20 min 3 times / week	PD, H	If too vigorous may worsen symptoms
Hydration	2 liters PO/day	PD	Edema
Salt	2-4 grams/day	PD	Edema
Fludrocortisone	0.1-0.2 mg PO daily	PD	Hypokalemia, hypomagnesemia, edema
Midodrine	5-10 mg PO TID	PD	Nausea, scalp pruritus, supine hypertension
Methylphenidate	5-10 mg PO TID	PD	Anorexia, insomnia, dependency
Bupropion	150-300 mg XL daily	PD, H	Tremor, agitation, insomnia
SSRI-Escitalopram	10 mg PO Daily	PD, H	Tremor, agitation, sexual problems
Pyridostigmine	30-60 mg PO BID	PD	Nausea, diarrhea
Erythropoietin	10,000-20,000 IV SQ weekly	PD	Pain at injection site, expensive
Octreotide	50-200 ug SQ TID	PD	Nausea, diarrhea, gallstones
Clonidine	0.1-0.3 mg PO BID; 0.1-0.3 mg patch weekly	H	Dry mouth, blurred vision
Labetalol	100-200 mg PO BID	H	Fatigue

PD = partial dysautonomic; H = hyperadrenergic; POTS = postural tachycardia syndrome

patients or 88 of 172 (51%) who were able to tolerate the drug. Fatigue (55%), palpitations (60%), presyncope (60%), and syncope (48%) were the most common symptoms that improved with pyridostigmine. Further, symptom reduction correlated with a statistically significant improvement in upright HR and diastolic blood pressure after treatment with pyridostigmine as compared to their baseline hemodynamic parameters (standing HR 94 ± 19 vs 82 ± 16 , $P < 0.003$, standing diastolic blood pressure 71 ± 11 vs 74 ± 12 , $P < 0.02$). Gastrointestinal problems were the most common adverse effects ($n = 39$, 19%) seen in our study.¹⁸

Severely affected and refractory patients may benefit from erythropoietin (EPO) therapy. EPO increases red cell mass, central blood volume and augments response of blood vessels to the angiotensin-II and thus causes vasoconstriction. These effects are quite useful in the treatment of orthostatic disorders. Prior to initiation of EPO therapy obtain a complete blood count (CBC), total iron binding capacity, serum iron and ferritin levels. Hematocrit (HCT) levels must be monitored and

should remain less than 50 on EPO. The starting dose is 10,000 units via subcutaneous injection once weekly. There is a 4-6 week delay between a given dose and the full clinical effect. The

hematogenic and hemodynamic affects are independent but may occur simultaneously. A goal HCT of low to mid 40 will often result in optimum hemodynamic augmentation. Monitoring during EPO therapy should include monthly CBC to document HCT less than 50. EPO therapy may infrequently result in a "serum sickness" type reaction characterized by nausea, fever, chills, and general malaise. In another study of 39 patients (age 33 ± 12 , 37 females) with resistant form of POTS, we reported sustained improvement in twenty-seven (71%) patients at mean follow-up of six month with EPO therapy. Eighty (21%) failed to respond to therapy while as 3 (8%) improved with therapy at 3months. Also, erythropoietin significantly improved sitting diastolic blood pressure but had no effect on other hemodynamic parameters.¹⁹ We reserve EPO therapy for patients that are refractory or intolerant of other

forms of treatment because of its considerable expense and subcutaneous route of administration.

Beta blocker therapy such as metoprolol tartrate may be beneficial in adolescent type POTS patients. In a single center retrospective study of 121 patients with possible POTS, written survey at follow-up were used to evaluate response to therapy with beta-blockers and midodrine. 47 adolescents responded to survey (Walker Functional Disability Inventory Survey) and reported improvement with a β -blocker (100% vs 62%, $P = 0.016$) and more attributed their progress to medication (63.6% vs 36.4%, $P = 0.011$) than did those treated with midodrine²⁰. In addition, beta-blocker therapy was associated with improved quality of life. Great caution should be taken in using beta-blocker therapy in a rare form of hyperadrenergic POTS secondary to the mast cell activation disorders. Octreotide is a somatostatin analogue with potent vasoconstrictive effects and is useful in the treatment of orthostatic disorders. In patients with resistant POTS, octreotide may be a useful as add on therapy. It is administered by subcutaneous injection 2-3 times daily. The starting dose is 50 ug and may be titrated up to 100-200 ug three times daily.

Agents that block the release or effect of norepinephrine (noradrenaline) are very effective for hyperadrenergic type POTS patients. We use clonidine starting at 0.1 mg orally twice daily and titrating up as needed. The patch form may be preferable to some patients and has the added benefit of providing a steady state drug release for one week. Labetalol, an alpha and beta receptor blocker, is also useful in this group of patients. Dosages of 100-400 mg orally twice daily are used. Methyldopa may have a role in highly selected patients with POTS. Symptom control may be improved with both the SSRI and SNRI classes of medications.

Inappropriate sinus tachycardia (IST) is an important confounding finding in suspected POTS patients. This syndrome is similar to hyperadrenergic type POTS. The clinical presentation may be similar with IST being more common in females. These disease states display and exaggerated response to isoproterenol infusion. It has been postulated that they may represent different states of the same pathologic process. A greater degree of orthostatic change in heart rate is seen in POTS patients. The supine rate rarely exceeds 100 bpm (IST will often be >100). Postural changes in serum norepinephrine levels are much more pronounced in POTS patients. It is important to differentiate POTS and IST. Radiofrequency ablation of the sinus node will rarely benefit hyperadrenergic POTS patients and will make PD POTS patients markedly worse.

Treatment of secondary POTS should focus primarily on the underlying disorder to the greatest extent possible. Diabetes mellitus or JHS related POTS are treated as PD POTS. Secondary POTS due to sarcoidosis or amyloidosis may benefit from steroid therapy. Secondary POTS that is paraneoplastic

may completely resolve with treatment of the underlying malignancy but may also respond to pyridostigmine.

Patients suffering from POTS have a disease that affects many aspects of their life. They are often unable to take advantage of meaningful employment or education opportunities. The pervasive life change experienced often results in significant psychosocial disruption as they may be excluded from social norms and certain environments. Frequently, patients require psychologists, social workers, and lawyers to address these aspects of living with POTS. The treating physician is a prominent and central figure who is a beacon of hope for this population. A positive, caring, and nurturing attitude may be the best medicine and lead to a rewarding rapport where an otherwise challenging disease exists.

Prognosis

There is limited data on the prognosis of POTS patients. Recent short term follow-up studies have shown better prognosis in patients with POTS.²¹ Roughly 50% of post-viral POTS patients make a meaningful recovery over about 2-5 years. Meaningful recovery may be defined as the absence of orthostatic symptoms and the ability to perform the activities of daily living with little or no restriction. Some patients experience a partial recovery and still others may demonstrate a progressive functional decline with time. As a general principle, a younger age of onset portends a better prognosis. A majority of patients tend to adopt different lifestyle modifications including increased fluid and salt intake to improve and reduce exacerbation of the POTS symptoms. In secondary POTS syndromes have a prognosis consistent with the underlying causative disorder.

Conclusion

Disruption of normal autonomic function may manifest as one of a heterogeneous group of clinical disorders collectively referred to as postural orthostatic tachycardia syndrome. Treatment is most successful when diligence has been taken to investigate the underlying disorder or POTS subtype and a comprehensive targeted treatment program is instituted with frequent follow up. Goals of care should focus on functional milestones and maintenance of function.

Competing Interests

None declared

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Over-the-counter and purchase-on-internet medications - Implications for psychiatry

Francis J Dunne , Mariam Omar , Nasser El-Hindy and Khalid Jaffar

An unquestioning belief in the power and efficacy of nature's healing remedies and processes, the placebo effect, disappointment and dissatisfaction with conventional medicines, outright rejection of orthodox treatments, convincing and persuasive advertising, reinforcement from others with similar views, endorsement by influential celebrities, perceived hand-me-down wisdom, bogus pseudoscientific claims, uncritical journalism, scare-mongering, feelings of desperation for a 'cure', and anecdotal case studies or surveys masquerading as research, are among the many reasons why patients and the public choose to alternative medicines either bought through local stores, pharmacies or on the internet. Over-the-counter drugs (OTCs) or over-the internet remedies are taken either with or without conventional medicines by millions of people every year and while most are harmless and safe to use there are inherent dangers of additive effects and interference with prescribed medications.

Benefits for patients who use OTCs include the convenience and sometimes less costly outlay on prescription drugs (analgesics, for example). Preparations may vary in price, according to the pharmaceutical provider. Self-treatment of minor ailments should theoretically lead to less pressure on GPs. Unfortunately, some patients tend to self-medicate for long periods (for example, analgesics) without visiting their GP for a health check to monitor the condition(s) for which they are using the OTC remedy to begin with. There is also the incorrect but widespread belief that because a prescription is not necessary to obtain these drugs they must be much less harmful than prescription-only preparations. Medicines may be used inappropriately, such as paracetamol for insomnia, or aspirin for stomach aches. Very often no record of OTCs is documented in the patient's notes. The list of OTCs is too numerous to cover in any detail here and for practical reasons the authors will concentrate on common legal products which most people are familiar with.

What causes the adverse effects?

An understanding of drug interactions gained momentum through the study of metabolizing enzymes. Cytochrome P450 inhibition or induction is probably the main mechanism for the pharmacokinetic interactions of drugs. CYP450 enzymes are haemoproteins (like haemoglobin) which comprise many

related though distinct enzymes referred to as CYP. Over 70 CYP gene families have been described so far and are further divided into families and subfamilies of which CYP1, CYP2 and CYP3, are involved in hepatic drug metabolism.¹ Thus, CYP3A denotes a cytochrome P450 enzyme that is a member of family 3 and subfamily A. It is abundant in liver and intestine. In the liver CYP450s are found mainly in the smooth endoplasmic reticulum. Any inhibition of CYP enzymes may result in enhanced plasma and tissue concentration of drugs, leading to toxicity. Likewise, induction may result in reduced drug concentration leading to decreased drug efficacy and treatment failure. Tricyclic antidepressants are substrates of 2D6 (CYP450 2D6 in full), which inactivates them by hydroxylation. For example, if a tricyclic antidepressant is given concomitantly with the serotonin/ noradrenaline reuptake inhibitor venlafaxine, the levels of the tricyclic antidepressant will rise because venlafaxine inhibits CYP450 2D6 and therefore prevents the breakdown of the tricyclic compound. Similar effects can occur with paroxetine, duloxetine, fluoxetine and atomoxetine. However, in clinical practice only atomoxetine requires dosage reduction when given with a 2D6 inhibitor.²

Diphenhydramine (a common ingredient in sleeping tablets) in therapeutic doses inhibits CYP450 2D6-mediated metabolism of venlafaxine in humans. Venlafaxine has a low potential to inhibit the metabolism of substrates for CYP2D6 such as imipramine and desipramine compared with several of the most widely used SSRIs, as well as the metabolism of substrates for several of the other major human hepatic P450s.³ Of all the marketed drugs, about 60% are metabolized by the CYP450 system. The presence of the latter in red blood cells and hepatocytes contributes to the first-pass metabolism of drugs. This will have add-on effects when CYP450 inhibitors are simultaneously ingested. For example, grapefruit juice inhibits this enzyme system and therefore the bioavailability of drugs taken by mouth will increase causing a reduction in first-pass effect (presystemic metabolism).⁴

Common varieties of OTCs

Many commonly used OTC preparations (other than food supplements and analgesics) contain the ingredient dextromethorphan (related to codeine), used to treat coughs,

colds and flu symptoms. Up to 125 different types of cold medicines contain dextromethorphan. It is an effective cough suppressant (antitussive) that works by raising the coughing threshold. It is not an analgesic. Cough syrups and tablet or capsule forms of medicine that contain dextromethorphan may lead to loss of coordination, dizziness and, nausea when used in high doses. Dextromethorphan is the d-isomer of the codeine analogue of levorphanol which mimics morphine. It is relatively nontoxic and its antitussive effects last for about 6 hours. It should be avoided when an MAO inhibitor is concomitantly given.

The generic term antihistamine refers in general to the H₁ receptor antagonists used for inflammatory and allergic conditions. Sedation is a prominent feature of the H₁ antagonist, diphenhydramine, used for allergies such as hay fever (short-term beneficial effect) and for symptomatic relief of the common cold. Guaifenesin, derived from the guaia tree, is a common ingredient found in cough expectorants. It is usually harmless though may cause problems in patients with compromised renal function. The mechanism of action, if any, is not known, save that it 'reduces viscosity' of respiratory secretions.

OTCs believed to help weight loss, such as laxatives, diuretics and diet pills, are often purchased either for genuine health concerns or for misuse. All have serious and potentially fatal side effects if taken for a long time, particularly electrolyte disturbances.⁵ Where diet pills are concerned problems may emerge insidiously with a few pills, quickly escalating to addiction. The alkaloid ephedrine is the principal active ingredient in the herb ephedra or ma huang. It is a potentially dangerous stimulant (sympathomimetic amine) contained in diet pills. Among the many possible side effects of diet pills are of course excessive weight loss with its attendant problems, alopecia, insomnia, and anxiety.

Used daily by millions of people worldwide, coffee and tea contain the methylxanthines caffeine and theophylline which act mainly by antagonism at purine receptors and by inhibiting phosphodiesterase. The effect is akin to a beta-adrenoreceptor agonist action. Caffeine is naturally found in certain leaves, beans, and fruits of over 60 plants worldwide. Its bitterness acts as a deterrent to pests. It can also be produced synthetically. Other than coffee and tea, the most common sources in the diet are cocoa beans, cola, and energy drinks. Product labels are required to list caffeine in the ingredients. Caffeine consumption in excess of 250mg daily produces symptoms indistinguishable from anxiety, including nervousness, irritability, tremulousness, muscle twitching, sleep disturbance, tachycardia, tachypnoea, palpitations, ectopic beats, and diuresis. A withdrawal syndrome can also occur and is associated with headache and a general muzziness. Caffeine may interfere with the effectiveness of drug treatment. For example, clozapine plasma levels can be raised, presumably through competitive inhibition of CYP1A2.⁶ In general terms,

an average cup of brewed coffee contains 100mg caffeine per cup, Red Bull 80 mg/ 250ml per can, tea 45mg/ cup, instant coffee 60mg/ cup and filter coffee 120mg of caffeine per cup. Excess consumption of Red Bull may cause myopathy due to caffeine-mediated hypokalemia and rhabdomyolysis.⁷

Paracetamol (acetaminophen in the USA) is metabolized in the liver. It is probably the most common household analgesic and is present in a variety of preparations and is usually well tolerated. Drugs that increase the action of liver enzymes which metabolize it for example, carbamazepine, isoniazid, and rifampin, reduce the levels of paracetamol and decrease its action. Doses greater than recommended may result in liver damage and in overdose a potentially fatal hepatic necrosis can occur.

Not much is known about the contents of home medication cabinets (HMCs), the management of leftover medications, and the inclination of patients toward self-initiated treatment using non-prescription drugs. One cross-sectional study conducted in 72 Belgian community pharmacies revealed that the most frequently encountered categories of registered medicines were NAIDs, nasal decongestants, and drugs used for nausea. Despite their high prevalence, NSAIDs and non-opioid analgesics did not predominate (14%) among the most frequently used drugs: food supplements were used daily in 23.3% of households. Twenty-one per cent of the drugs were expired, 9% were not stored in the original container, and the package insert was missing for 18%. Self-medication, although generally acceptable in terms of indication and dosage, was commonly practiced, also with prescription drugs. Taking into account that younger people showed a significantly higher rate of self-medication, awareness of the risks of self-medication is warranted.⁸

Relevance to Psychiatrists

Many psychiatric conditions are associated with excess alcohol use which complicates the picture when OTCs are used concurrently. Mixing alcohol with medication has the potential to cause nausea and vomiting, headaches, drowsiness, fainting, and loss of coordination. Because so many drugs can be bought without a prescription potential interactions with alcohol are often forgotten. Teenagers see OTCs as safer than illegal drugs and OTCs are sometimes taken to get a buzz or to help stay awake while studying. The home medicine cabinet allows quick access. Besides, parents will most likely have given an OTC preparation to their children for colds or other minor everyday ailments. Most drug education programmes however, focus primarily on illegal drugs, not OTC drugs and their potential for abuse.

Of some interest and importance to psychiatrists is the interaction when warfarin is combined with ginkgo (*Ginkgo biloba*) causing bleeding, a mild serotonin syndrome in patients who mix St John's wort (*Hypericum perforatum*) with serotonin-reuptake inhibitors. decreased bioavailability of

digoxin when combined with St John's wort, induction of mania in depressed patients who mix antidepressants and ginseng, exacerbation of extrapyramidal effects with neuroleptic drugs and betel nut (*Areca catechu*); increased risk of hypertension when tricyclic antidepressants are combined with yohimbine. Disulfiram which inhibits aldehyde dehydrogenase inhibits the metabolism of warfarin. Metronidazole causes an unpleasant disulfiram-like reaction when mixed with alcohol. Consumption of 6-8 glasses of grapefruit per day may raise levels of carbamazepine and pimozide. Grapefruit juice is thought to the metabolism of many drugs and inhibition can last a number of hours.⁹ The St John's wort component, hyperforin, contributes to the induction of CYP3A4. St John's wort also enhances the metabolism of other CYP3A4 substrates including the protease inhibitors indinavir and nevirapine, oral contraceptives, and tricyclic antidepressants such as amitriptyline. Other herbal remedies with the potential to modulate cytochrome P450 activity include ginseng, garlic preparations, and liquorice.¹⁰ Intake of St John's wort increases the expression of intestinal P-glycoprotein and the expression of CYP3A4 in the liver and intestine. The combined up-regulation in intestinal P-glycoprotein and hepatic and intestinal CYP3A4 impairs the absorption and stimulates the metabolism of cyclosporine, leading to subtherapeutic plasma levels.

The hormone melatonin plays a role in regulating the sleep-wake cycle but does not induce sleep *per se*. It is easily available through the internet and over-the-counter in the USA and many people use it for jet lag. Melatonin has side effects including diarrhoea, abdominal pain, headaches, nightmares, morning hangover, nausea, mild depression and loss of libido. Melatonin is used for many other complaints including tinnitus, depression, chronic fatigue syndrome (CFS), fibromyalgia, migraine and other headaches. Valerian root, a medicinal herb has been known to cause liver damage and should be used with caution. It too is most commonly used for insomnia and frequently combined with hops, lemon balm, or other herbs.

Many complementary medicines prescribed for anxiolysis/sedation (e.g. kava kava, valerian, passion flower and chamomile) are GABAergic, GABA (formed from glutamate) being the major inhibitory mediator in the brain, though for some, such as hops, the mechanism of action remains unknown. As expected, all remedies can lead to drowsiness when taken in high doses and can potentiate the effect of synthetic sedatives.¹¹ Kava has been taken off the market because of its hepatotoxicity.

Although sufficient dietary fibre and water are effective for the treatment of constipation some patients fear they are building up 'toxins' if they do not have 'regular' bowel habits. Often constipation is caused by opiate analgesics which are widely available, and in many cases patients are using antidepressant/psychotropic medication concurrently. The tendency to misuse laxatives is commonly seen in anorexia

nervosa though is not confined to that disorder. The osmotic laxative lactulose is a disaccharide of galactose and fructose and therefore care is needed where diabetic patients are concerned particularly if they are taking neuroleptic medications such as clozapine or olanzapine. Abdominal cramps and diarrhoea can occur with high doses. Laxatives have the potential to interfere with potassium levels, usually causing hypokalaemia.⁵

Ordinary foods and drinks may interfere with prescribed medications.¹² Grapefruit juice reduces the metabolism of calcium channel antagonists. Vegetables such as broccoli, cabbage, and Brussels sprouts are putative cytochrome P450 inducers and are known sources of vitamin K. Red wine, ethanol and cigarette smoke are also believed to induce the cytochrome P450 system and have the potential to interfere with the metabolism and catabolism of many drugs. Smoking interferes with clozapine metabolism. When smokers are prescribed clozapine abrupt smoking cessation may lead to high plasma concentrations with potentially serious consequences. Clozapine plasma concentrations can rise 1.5 times in the 2–4 weeks following smoking cessation,¹³ and in some instances by 50–70% within 2–4 days. Where baseline plasma concentrations are higher, particularly over 1 mg/litre, the plasma concentration may rise dramatically owing to non-linear kinetics. If patients smoking more than 7–12 cigarettes per day while taking clozapine decide to quit, the dose may need to be reduced by 50%.¹⁴ Smoking also interferes with duloxetine levels due to an induction of CYP1A2 by hydrocarbons contained in tobacco smoke. It cannot be expected that patients would be aware of these facts, let alone understand the pharmacology of the multitude of chemicals contained in OTCs.¹⁵

Availability does not mean harmless

Most people using OTCs are unaware of the potential for harm. Herbal remedies, for instance, with their attractive packaging, convey the impression of being beneficial merely because they contain 'earth minerals' and other 'natural ingredients:' therefore they must be beneficial for health, rather like eating vegetables or taking vitamins.¹⁰ There are numerous instances of drug interactions and many preparations may contain contaminants such as mercury, lead, and arsenic. One of the commonest ingredients in many lotions and potions is hydrocortisone, which if used liberally may cause skin atrophy. The most worrying aspect of OTCs is that they give hope to people with serious conditions which might be better treated with conventional medicines - multivitamins for cancer, mineral supplements for constipation, and so forth. With buzz words such as 'healing, energy, vitality, harmony, body balance, healthy living, total well-being, holistic', and 'traditional', targeting the sometimes gullible consumer, OTCs become very appealing. Others are taken in by the pseudoscientific jargon, 'healing powers, purifying the blood, eliminating toxins from the bowel', boosting one's immune system, and so forth. The outcome can be serious: for example, Chinese herbal medicines

containing extracts from *Aristolochia* plants have been implicated in the high incidence of urinary tract cancer in Taiwan, a study has suggested¹⁶ because aristolochic acid has a consistent pattern of inducing DNA damage.

Some patients may be coincidentally taking conventional, proven medicines yet attribute their improved health to the alternative remedy. Other beneficial factors which are often conveniently ignored include a change in diet, increased wellbeing through physical exercise, or going on holiday! There is of course, the natural remission of the illness, particularly with transient viral infections, or unexplained lower back pain, to cite two instances.¹⁷

Some common problems

Although the dangers of the common analgesics are relatively well-known (paracetamol causing liver damage, gastrointestinal upset with ibuprofen), patients are often unaware of the potential for adverse effects with other preparations. Nor are they always aware that many compounds combine two analgesics, for example, paracetamol and aspirin, or paracetamol and ibuprofen. Nonsteroidal anti-inflammatory drugs (NSAIDs) interfere with renal clearance and may result in elevated lithium levels with resultant toxicity.¹⁸ Combined use of an antidepressant or sodium valproate with an OTC could lead to abnormal liver function tests attributed solely to the former agents and not the OTC. Even reading the label does not guarantee insight and understanding of what is on offer. Labels are carefully and handsomely packaged by advertisers to persuade people their product is better than conventional medicines. Most consumers spend little time reading the labels about ordinary foodstuffs, never mind the chemical constituents of OTCs. In transplant patients, self-medication with St John's wort (*hypericum perforatum*) may lead to a drop in plasma levels of the immunosuppressant drug cyclosporine, causing tissue rejection. In the US, the Food and Drug Administration (FDA) with branches in other cities, including London (European Medicines Agency) approved a regulation in 1999 requiring that all OTC drug labels contain certain information such as ingredients, doses and warnings in a standardized format. This covers thousands of non-prescription products, including sunscreens. In the same way that people understand the nutritional value of foods, it is hoped that its efforts will help people use OTCs safely.

Sexual side effects are a frequent accompaniment of psychotropic drugs and patients are often bothered by impotence to such a degree they resort to surfing the internet to acquire sildenafil (Viagra) and the like. Such over-the-internet medicines are easy to acquire. Carbamazepine and St John's will decrease the level of sildenafil by competition with CYP3A4. Ketoconazole, the antifungal agent, works in a similar mechanism and may increase the levels of citalopram. Metronidazole has a disulfiram-like reaction with alcohol.

There is also the problem of addiction with OTCs because of ease of access to opioid compounds. Patients often do not perceive them as having addictive potential. Preparations containing ephedrine or dextromethorphan can be abused. Ephedrine is still used as a nasal decongestant. As an indirectly-acting sympathomimetic amine it can react dangerously with monoamine oxidase inhibitors because of the increased amount of noradrenaline stored in noradrenergic neurones. Opioids may be crushed and the powder snorted or injected leading to euphoria or elation, followed by addiction when compulsive use takes over. Patients may be subject to mood swings making underlying psychiatric disorders and drug treatment difficult to manage. Opioids produce drowsiness, and depress respiration in high doses. The combination with sedative psychotropic medication such as mirtazapine, olanzapine or quetiapine could be deleterious especially where there is concomitant weight gain. Buspirone (a 5-HT_{1A} receptor agonist used for anxiety) may interact with monoamine oxidase inhibitors (MAOIs), such as isocarboxazid, phenelzine, and tranylcypromine. Use of buspirone with these drugs can increase blood pressure. The combination of buspirone and trazodone may raise LFTs. The combination of buspirone and warfarin may accentuate the effects of warfarin and increase the risk of bleeding. Patients taking buspirone should not drink grapefruit juice, since even some time after a dose is taken, the amount of buspirone in the blood may be increased. Carbamazepine increases the metabolism of the pill reducing its effectiveness. The pill is more easy to acquire now (clinics and/or the Internet) and therefore unexpected pregnancies may occur in patients taking both. Cimetidine may increase the blood levels of sertraline by reducing its elimination by the liver. St John's wort interacts with the metabolism of the pill and this can result in unwanted pregnancies.

Overall OTCs are generally safe, though not where young children and pregnant women are concerned. Vitamins are safe unless taken in very high doses. Deficiency is rare in developed countries (apart from vitamin D) and therefore they are often taken unnecessarily 'to achieve balance' or for 'vitality and energy', and other eye-catching spurious claims. Glucosamine, an amino sugar, seems to be the most popular OTC dietary supplement for the treatment of osteoarthritis. It is naturally present in shellfish and in some fungi. Apart from occasional allergic reactions and mild gastrointestinal symptoms, it is generally innocuous, though conclusive evidence for its efficacy in osteoarthritis is lacking. Fish oil supplements usually come from mackerel, herring, tuna, halibut, salmon and cod. There is some evidence that omega-3-fatty acids contained in fish oils are beneficial for cardiovascular problems but more trials are needed. Side effects are minimal and include mild gastrointestinal upset.¹⁹

Doctors' dilemma

Is there a solution? Probably not, though one way to increase consumers' awareness of the dangers associated with OTCs

could be to change their status to match that of drugs such as simvastatin—they would still be sold over the counter, but with a pharmacist's supervision. The list of OTCs is rising leading to increased intake of phytochemicals in addition to the usual gamut of medicines used to treat upper respiratory infections. Potentially fatal interactions can occur with OTCs and traditional drugs. Providing better training for pharmacy staff, and restriction of the quantity sold per customer, should also be considered, though with so many retail outfits selling these products this is probably unrealistic. Besides, many of these products are available on the shelves, not necessarily at the pharmacy counter.

The most common addictions are combinations of opioids with standard analgesics. The Internet is an easy source for prescription drugs, increasing their availability and eliminating the need to see a doctor. Is there an epidemic of prescription opiate use? It is difficult to tell. Effective prevention, public information, and treatment policies require sound epidemiological data about drug use to ensure policy-making is not distorted by stories of celebrity arrests and media-generated hysteria which tend to give that impression that use of illegal drugs is rife. The lack of knowledge about the ubiquitous presence of unknown ingredients in OTCs may be a source of concern in the future when even more become easily available.

It is difficult for doctors and other health care professionals to advise patients on the effectiveness and safety of OTCs. The numbers of well-designed studies available for review are limited, often conducted in a small number of healthy participants, and for short time periods only.²⁰ A survey conducted by questionnaire in 238 follow-up UK rheumatology outpatients in three centers found nearly half (44%) had taken various herbal remedies or over-the-counter (OTC) preparations over the past 6 months. The most commonly used were: cod-liver oil, glucosamine, and/or chondroitin, and evening-primrose oil. Rheumatology outpatients have a particularly high risk of interactions with conventional medication because of polypharmacy and comorbidity. Ginkgo biloba, devil's claw, ginger, and garlic may have antiplatelet or anticoagulant effects and may exacerbate the gastrointestinal bleeding risk of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Echinacea (taken by 4%) may be hepatotoxic and could exacerbate the adverse effect of disease-modifying antirheumatic drugs (DMARDs). Most patients are unaware of the potentially harmful interactions.²¹

The authors carried out a small audit of consecutive outpatients and staff on a random basis seen in our unit. Of the 45 people who completed the questionnaire 70% affirmed use of OTCs, either presently or in the past. A high percentage (73%) had never been asked by their GP about these 'alternate medicines' and among health professionals 25% never enquired from patients about the use of OTCs. More than half (63%) were unaware of possible side effects before taking them and nearly 50% had not considered that the OTCs might interact with

prescribed medication. As would be expected, the majority of users (84%) did not experience any side effects. Nonetheless 16% experienced unpleasant adverse effects such as tachycardia, nightmares, drowsiness, cough, constipation, and exacerbation of asthma. When asked who had recommended the preparation/s the response was generally, 'friends' or 'I knew about it myself'. When asked why they bought it over-the-counter, the response was 'just in case I need it', 'cheaper than prescription' 'it is a natural remedy' 'it's only Nurofen'. As with most surveys, the commonest preparations were analgesics, laxatives, glucosamine for arthritis, and decongestants. Others bought OTCs to promote good health because they are herbal and natural', for example, ginkgo biloba. In a separate random survey of 50 consecutive outpatients carried out by FJD and N El-H, some 40% were taking herbal remedies.

Conclusion

Medical care has become fragmented in recent years. The family doctor of old no longer acts as a gatekeeper to coordinate medications patients are prescribed. A gynaecologist may prescribe the pill to a patient and a walk-in clinic may prescribe an antibiotic to the same patient. How does a doctor inform the patient that antibiotics decrease the effectiveness of the pill if the doctor is unaware of the myriad of other supplements including OTC medications, a patient is taking? Although a patient should bear some responsibility, in reality he/she may not have the expertise to discern the complications and interactions of medications. Besides multiple use of preparations is more often a problem of older age groups who frequently have many health problems. The family pharmacist has also been lost to mail-order pharmacies and sometimes suspect internet web sites. Because of the increase in numbers of prescriptions and OTCs, doctors and pharmacists are using computer programs to establish what is safe and what is not.

Strategies to mitigate these problems could include more general enquiries about prescriptions, OTC, and herbal drug use at the initial examination.²² Even though some patients may be aware of the potential for drug misuse, others are naive and do not realize the harm involved. Providing containers to enable patients to dispose of unused or unneeded prescriptions or OTC medications is another tactic. Treating the underlying causes (of pain, for example) more aggressively may obviate the need for patients adding OTCs to their drug list. Practicing careful record keeping of prescription refills and tightening controls over prescription blanks are other practical measures. Where patients have become addicted to medications, programmes such as Narcotics Anonymous may help.

None declared

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Risk of Breast Cancer due to Hyperprolactinemia caused by Antipsychotics (Neuroleptics)

Umesh Vyas

ABSTRACT

Breast cancer is the most common cancer in females, and is the second most common cause of death. There are several factors which increase a woman's risk for the development of breast cancer. Some reports suggest that neuroleptics and other dopamine antagonists increase the risk of breast cancer due to hyperprolactinemia. There are other reports which suggest that they may decrease the risk of cancer especially rectum, colon and prostate. Additionally, there is evidence that patients with Parkinson's disease have lower rates of breast cancer and other types of malignancies.

KEYWORDS: Hyperprolactinemia, Antipsychotics, Breast cancer

Introduction

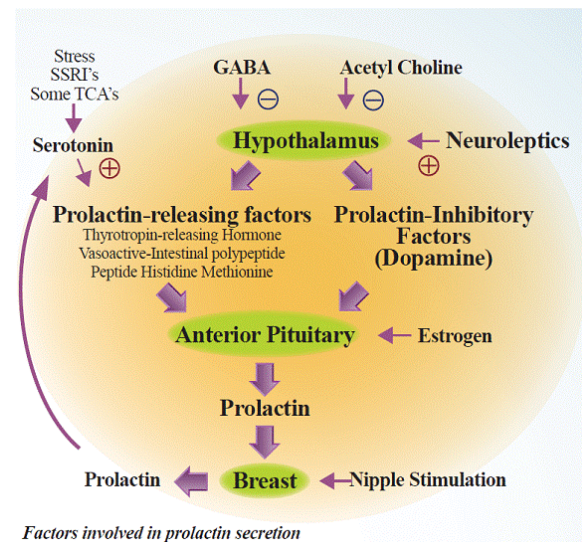
Prolactin is a polypeptide hormone that is secreted by lactotrophs of the anterior pituitary gland. Prolactin secretion shows a circadian rhythm¹, with highest levels occurring during the night and the nadir occurring during the afternoon and evening. The best known function of prolactin is the stimulation and maintenance of lactation.

Normal basal levels of serum prolactin are approximately 20 to 40 ng/ml in women (depending on the phase of their menstrual cycle), and 15 ng/ml in men. However, these concentrations can also vary with age. Hyperprolactinemia is diagnosed when serum prolactin concentrations are >20-25 ng/ml (400-500 mU/l) on two separate occasions³.

Hyperprolactinemia is the most common disorder of the hypothalamic-pituitary-gonadal (HPG) axis⁴ and can have physiological causes - pregnancy, nursing, sleep, stress, sexual intercourse or pathological causes - tumor called prolactinoma. Multiple factors are involved in prolactin secretion (Figure 1). However, hyperprolactinemia is also a common side-effect of traditional antipsychotics (e.g. haloperidol) and is associated with the use of some newer second generation agents^{2, 6}.

The prevalence of hyperprolactinemia is low in the general population (0.4%), but it can be as high as 9 to 17 % in women with reproductive disorders. The disease occurs more frequently in women than in men, multiple signs and symptoms associated with hyperprolactinemia (Table 1).

Multiple variables affect probability of development of breast cancer (Table 2) and a number of important factors determine the risk for breast cancer, and the most important of these seem to be related to estrogen and possibly prolactin (Table 3).



Factors involved in prolactin secretion

Figure 1: Factors involved in Prolactin secretion

Table 1: Signs and Symptoms of Hyperprolactinemia

- Gynaecomastia
- Galactorrhoea
- Infertility
- Menstrual irregularities: oligomenorrhoea, amenorrhoea
- Sexual dysfunction: decreased libido, impaired arousal, impaired orgasm
- Acne and hirsutism in women (due to relative androgen excess compared with low estrogen levels)
- Behavioural effects
- Decreased bone mineral density (BMD) which may lead to increased risk of osteoporosis.

Table 2: Probability of Developing Breast Cancer³²
Risk of Breast cancer

Variables	Increased	Decreased
Age	Older	Younger
Socioeconomic status	Higher	Lower
Family history of breast cancer	Present	Absent
Racial	Caucasian	Oriental
Geographic	America	Asia
Marital status	Single	Married
Age at first pregnancy	Older	Younger
History of multiple pregnancies	Present	Absent
Age at menarche	Younger	Older
Age at natural menopause	Older	Younger
Artificial menopause	Absent	Present

Table 3: Epidemiology of breast cancer⁷

- Age of menarche
- Late pregnancy
- Obesity
- Caucasian females have slightly higher incidence
- The highest incidence of breast cancer occurs after age 35, with 83% of the cases occurring after age 50 and only 1.5% under age 30
- 1 in 11 women will develop breast cancer sometime during their lifetime
- The highest incidence of breast cancer in the US is found in the northeastern part of the country
- The women with previous cancer of one breast are at risk for cancer in the opposite breast
- A woman whose natural menopause occurs before age 45 has only half the breast cancer risk of those whose menopause occurs after the age of 55⁷.

Methods

Pubmed.gov searched by using keywords

Antipsychotics and Hyperprolactinemia

Hyperprolactinemia is caused by these agents by blocking D2 receptors on lactotrophs and thus preventing inhibition of prolactin secretion. Furthermore, it has been suggested that the degree of elevation of prolactin correlates with the degree of occupation of D2 receptors in excess of 50%⁸.

Most studies have shown that conventional antipsychotics are associated with a two to tenfold increase in prolactin levels^{9, 10}. In general, second generation antipsychotics produce a lower increase in prolactin than conventional agents. Among second generation antipsychotics associated with increased prolactin are amisulpride, zotepine and risperidone^{11, 12, 13}.

Antipsychotic induced Hyperprolactinemia and Breast cancer

Prolactin is known to increase the incidence of spontaneously occurring mammary tumors in mice¹⁴ and increase the growth of established carcinogen-induced mammary tumors in rats¹⁵.

Prolactin and other sex hormones such as, estradiol and progesterone are important in normal mammary gland growth and development as well as lactation. Both animal and *in vitro* data suggest that prolactin is involved in tumorigenesis by promoting cell proliferation, increasing cell motility, and improving tumor vascularization. Whereas prolactin and its receptor are found in normal and malignant tissues, concentrations of both are generally higher in malignant tissue¹⁶.

Several studies have linked hyperprolactinemia to an increased risk of breast cancer in women^{17, 18}. Mechanisms that have been suggested to explain this possible action of prolactin include the increased synthesis and expression of prolactin receptors in malignant breast tissue and a prolactin-induced increase in DNA synthesis in breast cancer cells *in vivo*¹⁸.

One of the hypothesized roles of prolactin in the development of mammary tumors is to create mammary gland conditions favorable for the action of carcinogens through its stimulation of the rate of mammary gland DNA synthesis, a measure of the frequency of mammary gland cell division¹⁹.

Several epidemiological studies have investigated whether female psychiatric patients receiving treatment with antipsychotics have a higher incidence of breast cancer but results have been conflicting. However, the most recent and methodologically strong study, found that antipsychotic dopamine receptor antagonists conferred a small but significant risk of breast cancer. This study had a retrospective cohort design and compared women who were exposed to prolactin-raising antipsychotics with age-matched women who were not²⁰.

Conversely, other studies have shown no correlation between hyperprolactinemia and breast cancer^{21, 22}. Furthermore, as most breast cancers are thought to be fueled by estrogen²³, and hyperprolactinemia causes estrogen deficiency²⁴, it is perhaps surprising that hyperprolactinemia has been linked with an increased risk of breast cancer. Indeed, post-operative hyperprolactinemia in breast cancer patients has been shown to improve disease free and overall survival. Obviously, more studies are necessary to define any possible links between hyperprolactinemia and breast cancer.

In view of these problems it would be of interest to go around the contentious issue of possible carcinogenic effects of dopamine antagonists using a classical condition of dopamine loss or attenuation as in Parkinson's disease (PD). Using computerized registers of death data of the National Center of Health Statistics for years 1991 through 1996, estimated

12,430,473 deaths of persons over forty, and extracted 144,364 cases with PD. Tellingly, PD patients showed a highly significant reduction of overall cancer incidence. PD resistance to breast cancer might conceivably be attributed to dopaminergic treatment antagonizing hyperprolactinemia^{26, 27, 28}.

Another recent study showed that dopaminergic therapy inhibits angiogenesis thereby acting as an anti-tumor agent²⁹.

Epidemiological studies of women who have received prolactin-releasing drugs such as reserpine and perphenazine have not disclosed increased risk³⁰.

Antipsychotic induced Hyperprolactinemia and Other cancers

Antipsychotics have been hypothesized to account for the reduced cancer occurrence observed in patients with schizophrenia in a number of studies. This reduction has been found primarily in men in smoking-related cancers, and in prostate and rectal cancer.

In addition, a study found a reduced risk of rectal cancer in both men and women as well as indications of a reduced risk of colon and prostate cancer in this population-based cohort of neuroleptic users. Reassuringly, they observed no increased risk of breast cancer in female users³¹.

Comments and recommendations

- Hyperprolactinemia results from treatment with any drug that disrupts dopaminergic function on the HPG axis and is not limited to the use of antipsychotics.
- Management of supposed anti-psychotic associated hyperprolactinemia should exclude all other causes, involve regular monitoring of adverse effects and include a regular risk-benefit discussion with patient.
- Switching the patient to prolactin-sparing antipsychotic (i.e. Aripiprazole, Olanzapine, Quetiapine or Clozapine) usually proves effective, though there is also a risk of relapse.
- It seems prudent to avoid prescribing prolactin-raising antipsychotics in patients with past history or family history of breast cancer.
- It is premature to mandate warning patients of an unknown and undemonstrated increase in the risk of developing breast cancer associated with neuroleptic treatment.
- Before initiating antipsychotic treatment a careful examination of patient is necessary.
- One should examine the patient for evidence of sexual adverse events, including menorrhagia, amenorrhoea, galactorrhoea and erectile/ejaculatory dysfunction. If evidence of any such effects is found, then the patient's prolactin level should be measured.

- Patient history, physical examination, pregnancy test, thyroid function test, blood urea and creatinine level can help determine if other etiologies are responsible.
- Presence of headache and visual field defects is suggestive of a sellar space-occupying lesion (MRI indicated), but the absence of these features does not exclude such pathology.
- History of menstrual cycling (duration, amount and intervals of menstruation) as well as lactation and sexual functioning should be taken before antipsychotic medication is initiated.
- Obtain a pretreatment prolactin level, which one can compare with subsequent samples if the patient develops symptoms associated with relatively modest hyperprolactinemia.
- The risk-benefit ratio for treatment of antipsychotic-induced hyperprolactinemia needs to be assessed on an individual basis.
- If there is doubt about the cause of the hyperprolactinemia, patient should be referred to an endocrinologist.

Current recommendation

A rise in prolactin concentration should not be of concern unless complications develop, and until such time no change in treatment is required.²⁰

Conclusions

There is no definitive data suggesting increased risk of breast cancer available at this time, thus author concludes:

- Further prospective studies are needed in this area, with large number of patients, before a more definitive answer can be provided.
- Detection of existing mammary tumor by breast examination or studies (mammogram) is recommended prior to administration of neuroleptics.
- Development of newer antipsychotic drugs that do not increase serum prolactin level may be indicated.

Strengths

- Each article found by search term was reviewed
- Data were extracted from each article to find answer of research question
- Pubmed.gov is a huge database for search.

Limitations

- This literature review has been conducted by a single author, thus bias on part of author cannot be ruled out
- Author was limited by time to review articles available in other databases.

Key Points

- Most studies report no increased risk of breast cancer associated with use of these medications.
- Only one study reported a positive correlation between neuroleptic induced hyperprolactinemia and increased risk of breast cancer.
- Other studies report inconclusive data.
- At this time we do not have definitive data suggesting increased risk of breast cancer secondary to hyperprolactinemia caused by antipsychotics.
- Further prospective studies are desirable.
- Author concludes that thorough screening of patient should be best

Competing Interests

None declared

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Synchronous paraspinal and hepatic hydatid disease ; a rare presentation

Ashish S Motewar, Sayalee S Narwade and Mandar R Tilak

ABSTRACT

Hydatid cystic disease is a common zoonotic infection in the Indian subcontinent. However in the following case we report a rare presentation found in a young patient synchronously in the paraspinal and intrahepatic location without intercommunication. A high index of clinical suspicion is necessary for diagnosis. Hydatid disease is to Echinococcus species commonly granulosus, sometimes multilocularis. The common locations of hydatid cysts are the liver (65% to 75%) and lungs (25%-30%). Hydatid disease rarely develops in locations such as spleen, kidney, bones, heart, brain, peritoneum, myocardium and muscles (1-4%). A 25 year old male presented with complaining of backache on the right and fullness in the right paraspinal region. On clinical examination he had a non ballotable lump in right paraspinal region within intra muscular plane extending from posterior subcostal margin to iliac region. CT abdomen (P+C) revealed a well defined hypodense non-enhancing cystic lesion in the right lobe of the liver with peripheral calcification with lesion of similar morphology in right paraspinal muscles. Exploration of the right paraspinal region was done. Cyst was beneath the oblique & latisimus dorsi, superficial to psoas muscle without invasion in it. Cyst opened multiple daughter cysts along with pus evacuated. Cyst excised in toto without spillage. Hydatid cyst is frequently asymptomatic, most prevalent in sheep and cattle-breeding areas. The cysts can not easily grow in muscles due to their contractility and lactic acid content. The latent period of cyst development varies between 5-20 years. Surgery is the optimal treatment for hydatid cysts. Open cyst evacuation is indicated for gharbi types 4&5, posterior cysts, central cysts, more than 3 cysts, infected cysts, biliary communication, pulmonary communication & peritoneal rupture. Alternative therapy with non-toxic scolocidal agents or combination chemotherapy has been advocated in the management of recurrence and high risk of contamination.

Introduction

Hydatid disease is due to Echinococcus species commonly granulosus sometimes multilocularis. The common locations of hydatid cyst are the liver (65% to 75%) and lungs (25%-30%)^{1,2,3}. Hydatid disease rarely develops in some locations such as the spleen, kidney, bones, heart, brain, peritoneum, myocardium and muscles (1-4%)¹. In our review of literature, concomitant paraspinal and intrahepatic hydatid is reported rarely.

Case Report

A 25 year old male presented with backache on the right for 1 month and fullness in the right paraspinal region. No history of trauma, fever, burning micturition, pain in abdomen, weight loss or hematuria.

On clinical examination he had non ballotable lump in the right paraspinal region, measuring 15x5x5cm with ill defined margins intra muscular plane extending from the posterior subcostal margin to the iliac region with no overlying skin changes and no organomegaly.

Blood investigations including liver function tests and kidney function tests were normal. Ultrasound examination revealed hepatomegaly with thick walled cystic lesion in the right lobe of the liver and the in muscle plane in the right renal angle region.

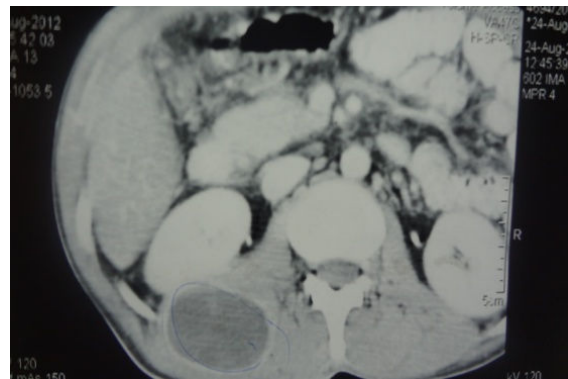


Figure 1: Right paraspinal hydatid

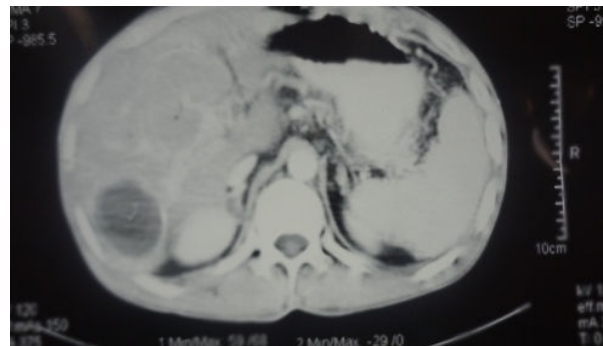


Figure 2: Intrahepatic hydatid

CT abdomen (P+C) revealed a well defined hypodense non-enhancing cystic lesion measuring 45x40 cm seen in the right

lobe of the liver with peripheral calcification with another lesion of similar morphology of size 14x5x3.6cm in the right paraspinal muscles with no intercommunication between them and no bone, spinal canal alteration or compression of the right kidney.

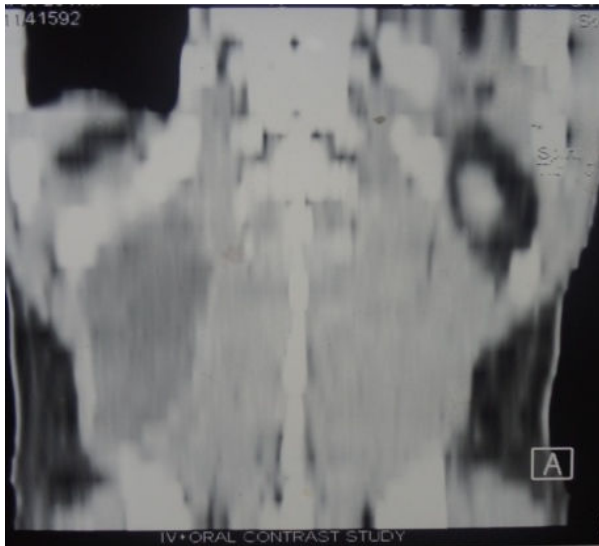


Figure 3: Coronal view of CT image

The diagnosis of paraspinal hydatid cyst was confirmed. As the patient was symptomatic for paraspinal hydatid cyst only and the size of the hepatic cyst was small, exploration of the right paraspinal region was done after 21 days of antiscolicidal treatment. There was a cyst measuring 15x5x5 cm beneath the oblique and latisimus dorsi, superficial to the psoas muscle without invasion into it. The cyst opened multiple daughter cysts along with pus evacuated. The cyst excised in toto without rupture & spillage. Negative suction drain was kept. Post operatively on day 3 the drain was removed, stitches removed on day 10 and discharged. Histopathology confirmed diagnosis.

Discussion

Hydatid disease is most prevalent in sheep and cattle-breeding areas, which is where the first step in the chain of transmission occurs. The causative agent is introduced to the dog (the primary host) through the faeces of livestock. The minute larval form of *E. granulosus* lives in the small intestine of the dog species. The eggs are passed in the faeces of an infected dog and can be transferred to mammal (man – intermediate host) that ingests them. After ingestion, the embryos are released from the eggs, traverse the intestinal mucosa and disseminate systemically via venous and lymphatic channels and develop into hydatid cysts in various body parts.

The cysts cannot easily grow in muscles due to their contractility and lactic acid content. The wall of a cyst in the muscle is formed by three layers: the inner germinative, intermediate and outer granulomatous adventitial layer. The most common skeletal sites include hip, thigh, shoulder and

humerus regions. Hydatid cysts are frequently asymptomatic¹. The latent period of cyst development varies between 5 and 20 years^{4,5}.

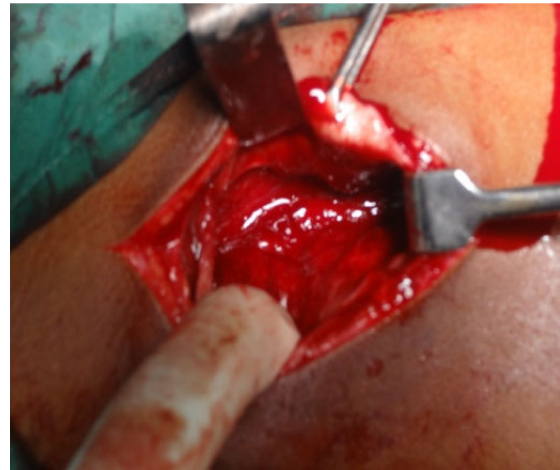


Figure 4: Intraoperative photograph

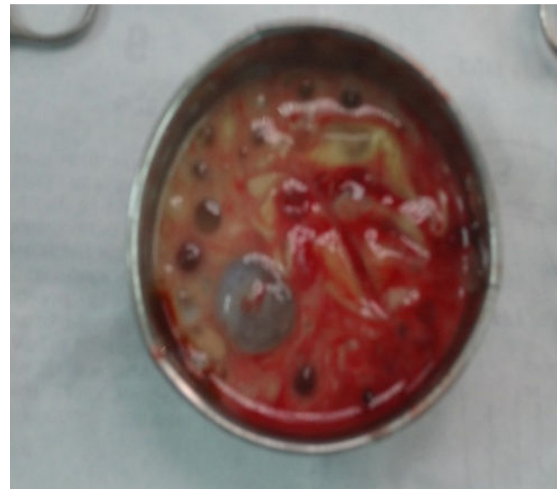


Figure 5: Photograph of multiple daughter cysts

Serological tests are widely used to diagnose hydatid cysts. However, positive serological results do not confirm, nor negative results exclude the disease^{1,6}. The imaging features of hydatid cysts are well described in the literature. Ultrasound scans are a sensitive, safe, non-invasive method. It is the procedure of choice for the diagnosis of cysts with a “honeycomb” pattern (type 3), as observed in our patient. Gharbi’s classification provides morphological description on ultrasound. Type 1-pure fluid collection, type 2-fluid collection with split wall (floating membrane), type 3-fluid collection with septa, type 4-heterogenous echographic pattern, type 5-reflecting thick walls.

As seen in our case the cyst fluid appears anechoic at USS, yields an attenuation value of 3-30HU at CT. Calcifications in the cyst wall as in our case are best detected on CT scans. CT has the advantage of detecting smaller cysts when located outside the liver and sometimes differentiating parasitic from non-parasitic cysts, for follow-up studies during chemotherapy.

Other diagnostic means such as fine needle aspiration should be avoided because of dangerous anaphylactic reactions⁷.

Surgery is the optimal treatment for hydatid cyst. Open cyst evacuation is indicated for gharbi types 4 & 5, posterior cysts, central cysts, more than 3 cysts, large cysts, heavy calcification, infected cysts with above criteria, biliary communication, pulmonary communication and peritoneal rupture. Laparoscopic evacuation is indicated in Gharbi type 1 or 2, anterior cysts, peripheral cysts, 1-3 cysts, small cysts, no or minimal calcification. Pericystectomy is complete resection of cyst wall without entering the cyst cavity.

Alternative therapy with non-toxic scolocidal agents or combination chemotherapy using imidazole derivatives, particularly albendazol, has been advocated in the management of patients with recurrence and high risk of contamination⁸.

Competing Interests

None declared

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Drug Interactions with Grapefruit Juice

Nadeem Mazi-Kotwal and Madhavan Seshadri

ABSTRACT

Grapefruit juice sales are gradually increasing since 1970s and reached an average of 24.9 million litres per annum between 2004 and 2007. The use of grapefruit juice on its own or in a mixture with other juices is gradually increasing in UK and grapefruit juice is now a regular part of breakfast consumption in most of Western Europe and America.

Since the accidental discovery of its interaction with felodipine, more than 85 drugs have been identified to have the potential to cause serious adverse reactions. However there has been a lack of awareness of its effects on other medications in patients as well as physicians. It is necessary for all medical practitioners to be aware of the potential for enhanced serum levels of the affected drugs and the possibility of serious adverse effects.

Grapefruit juice inhibits the CYP3A4 enzyme of the cytochrome P450 system in the intestinal mucosa, increasing the bioavailability of drugs with a high first pass metabolism. Therapeutic doses of the affected drugs may produce serious adverse reactions. More research is necessary to identify the mechanism of such interactions and to identify the active ingredients.

Introduction

Grapefruit (*Citrus paradise*) is thought to have originated as a cross between the Jamaican sweet orange (*Citrus sinensis*) and the Indonesian pomelo (*Citrus maxima*) fruit. It was first bred in Barbados and brought to Florida in 1820s. Subsequently, different mutant and hybrid varieties were developed. Although the white and pink varieties were being popularly consumed, the ruby red variety has become very popular and commercially successful.

The taste is a mixture of the sweetness and tanginess of an orange and the sourness of a citrus fruit. It is a rich source of vitamins C and potassium. It is found to have antioxidant properties due to the presence of lycopene¹ and an ability to inhibit atherosclerosis due to the presence of pectin^{2,3}. The seed extract is thought to have antimicrobial and antifungal properties.

With good publicity, marketing and coverage by health magazines, grapefruit juice has gained widespread use and in most Western Europe and America it is one of the common fruit juices consumed at breakfast. In the United Kingdom, in terms of fruit juice sales, it ranks second among citrus fruits and the fourth overall.⁴

Pharmacokinetic effects

The interaction of grapefruit juice with medication was first reported by Bailey et al in 1991 after their accidental discovery

of up to four fold increase in the blood levels of filodipine when taken with grapefruit juice⁵. Further studies have identified similar interactions with more than 85 drugs⁶. The half life of the effects of grapefruit juice is estimated to be around 12 hours⁷, but these effects may last from 4 hours to 24 hours⁸. The effects are more pronounced with regular consumption of grapefruit juice prior to ingestion of the drug and there can be a cumulative increase in drug concentrations with continued grapefruit juice intake^{7,9}.

As little as 200-250ml may be sufficient to induce its effects¹⁰. Some of the interactions involve medication that have narrow therapeutic window and can therefore cause potent adverse effects such as torsade de pointes, rhabdomyolysis, myelotoxicity, respiratory depression gastrointestinal bleeding, nephrotoxicity and sudden cardiac death.⁶ There is a lack of awareness among both doctors and patients about its effects and interaction with various medications.

Mechanism of action

These pharmacokinetic interactions with grapefruit juice are more observable in drugs with high first pass metabolism and in those with an innate low oral bioavailability. The oral bioavailability of affected drugs is increased but their half life usually remains unaltered^{11,12}. Grapefruit juice is associated with the inhibition of Cytochrome P450 enzyme system, particularly the CYP3A4 enzyme⁷. The CYP3A4 enzyme is present both in the liver and intestinal mucosa. Once the drug is taken up by the mucosa, the susceptible drug may be metabolised by the

CYP3A4 or pumped back into the intestine lumen by P-glycoprotein. The observed effects of grapefruit juice are thought to be mainly due to the inhibition of intestinal CYP3A4 activity, which leads to decreased first pass metabolism and hence increased bioavailability. This inhibitory action is fairly quick and may be due to the rapid degradation of the enzyme or any decrease in its production from the mRNA. The production of mRNA itself from DNA is not thought to be affected¹³. The susceptibility varies between individuals depending upon their genetic expression of CYP3A4, the effects being more prominent in those with high small intestinal CYP3A4 content^{7, 14}.

Table 1: Potential risk of drug interactions with grapefruit juice^{6, 7,13,25,26,27}

Group	Drug	Risk of Interaction		
		V High	High	Mod
Anaesthetic	Ketamine	+++		
Anaesthetic	Alfentanil		++	
	Fentanyl		++	
Antiarrhythmic	Dronedorone	+++		
	Amiodorone		++	
	Quinidine			+
Anti-Cancer	Dasatanib		++	
	Everolimus		++	
	Nilotinib		++	
	Pazopanib		++	
	Sunitinib		++	
	Vanetanib		++	
Antidepressants	Buspirone		++	
	Sertraline			+
	Clomipramine			+
Antiemetic	Domperidone	+++		
Antiepileptics	Carbamazapine		++	
Anti-HIV	Maraviroc	+++		
	Ripivirine		++	
Anti-infective	Erythromycin		++	
	Quinine		++	
	Primaquine		++	
Antiplatelet	Clopidogrel		++	
Antipsychotics	Pimozide		++	
	Quetiapine		++	
	Ziprasidone		++	
Benzodiazepines	Midazolam			+
	Diazepam			+
	Triazolam			+
Ca-channel bolckers	Felodipine			+
	Nifedipine			+
Immunosuppressants	Cyclosporin		++	
	Tacrolimus		++	
	Sirolimus		++	
Opioids	Oxycodone		++	
	Methadone		++	
Statins	Simvastatin	+++		
	Atorvastatin		++	
Urinary Tract	Solifenacin			+
	Fesoterodine			+
	Darifenacin			+
	Tamsulosin			+

The effect of grapefruit juice on the P-glycoprotein is unclear. The activation of P-glycoprotein pumps the drug back into the

intestinal lumen which should reduce bioavailability and similarly the inhibition of P-glycoprotein increases the bioavailability. Some studies suggest that the inhibition of P-glycoprotein is the mechanism responsible for the increased bioavailability of certain drugs like cyclosporine^{15,16}.

The active ingredients responsible for interactions of grapefruit juice with medication are not clearly identified. The compounds exerting this action are thought to be either the flavanoids such as naringin and naringenin^{17,18,19,20} or the furanocoumarins such as bergamottin and its derivatives^{21,22,23,24}, but there is no clear consensus.

Drug interactions

Table 1 below lists some of the commonly used drugs whose bioavailability is affected by grapefruit juice. Although the best known interactions have been mentioned in the table, there are many other drugs like carvedilol, estrogens, itraconazole, losartan and methyl prednisolone whose bioavailability is increased by grapefruit juice and the adverse effects are not yet clear.

Implications on clinical practice

Clinicians should make themselves aware and educate their patients of these potential interactions, keeping in mind the individual variations in susceptibility. This may be particularly important for medications that have a very narrow therapeutic window, medication that have an innate low oral bioavailability and a high first pass metabolism mainly via CYP3A4.

A patient may develop exceptional beneficial effects or equally, significant adverse effects should he start consuming grapefruit juice mid- treatment. Conversely, a drop in efficacy of a drug is also possible, should a patient using grapefruit juice on a regular basis, stops it suddenly.

To achieve steady concentration of the medication and avoid such potential effects, it may be best to advise patients to avoid consuming grapefruit juice if there is a potential of interaction. The half life of the effect of grapefruit juice appears to be around 12 hours and therefore, it is advisable to discontinue grapefruit juice 72 hours prior to starting any drug with potential interactions.^{8,9}

Due to the prolonged effect of CYP3A4 inhibition which may last up to 24 hours, it is not possible to avoid these interactions by separating the times of drug and grapefruit juice consumption.^{8,9}

There is more research needed to clarify the mechanism of action and to determine the active ingredients. The identification of the active ingredient can allow oral administration of drugs that undergo CYP3A4 mediated high first pass metabolism because of which currently, they can only be given systemically.

In light of the possible increase in bioavailability of specific drugs, although it might be possible for patients to use this to their advantage in reducing the dose of their medication under medical supervision, it is perhaps too early to recommend the use of grapefruit juice as an adjunctive or augmentation strategy.

Competing Interests

None declared

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Hypertension: How To Work With Patients To Get The Perfect Blood Pressure

Ruth St John and Daljit Singh Sura

Incidence and Prevalence

The incidence and prevalence of hypertension is rife among first and second world countries and arguably, could be labelled the most common chronic disease in the UK¹. It is estimated that a quarter of all adults in the UK have hypertension². This is alarming in light of the incredible contribution of hypertension to mortality and morbidity. Evidence shows that for each 2mmHg rise of systolic blood pressure, mortality from ischaemic cardiac events rises by 7% and mortality from ischaemic intracranial events rises by 10%^{3,4}. The key to reversing this lies in diagnosing hypertension accurately and quickly and knowing how to best treat each patient.

Understanding hypertension

It is still not entirely clear what mechanisms cause hypertension. Evidence has proven that systolic blood pressure increases in a linear fashion with age, which is due to the loss of elastic tissue in arteries with age^{1,5}. This is known as 'essential hypertension'. The majority of patients who are diagnosed with hypertension have 'essential hypertension', in other words, there is no clear cause found besides increasing age^{1,2}. Research has shown that other factors can be associated with hypertension but alone may not necessarily cause it. Unalterable risk factors include genetic predisposition, age, sex and race. Other factors which have proven to raise blood pressure include environmental factors such as lifestyle and diet, obesity (randomised control trials have shown that a weight loss of one kilogram can be attributed to one mmHg fall in diastolic blood pressure⁵), excessive alcohol intake, smoking, stress at work or in the home, socio-economic status and recent major life events^{1,2,6}.

How to take the perfect blood pressure

In the clinic setting, make sure the patient is relaxed, sit the patient comfortably with their arm outstretched, resting on the table and wait a few minutes. Make sure the sleeves are not too tight as this will alter the readings^{1,5}. Be careful that the blood pressure cuff is the correct size for the patient as small cuffs can give a false high reading for larger patients and larger cuffs can give a false low reading for smaller patients^{3,5}. Check the pulse is regular as irregular pulses can give incorrect readings from automated devices - if in doubt perform it manually⁵. Take the blood pressure in both arms and repeat several times, discard

the first reading and always record the lowest reading in the patient's file¹.

The well recognised 'white coat syndrome' has a prevalence of about 10% in the UK and according to NICE data, the syndrome can cause a difference of 20/10mmHg between readings in a clinical setting and those at home^{1,3,5}. In light of this, NICE altered the guidelines in 2011, stating that any patient with a reading close to 140/90mmHg is to be sent home with an Ambulatory Blood Pressure Monitor (ABPM)³. This is a device attached to the patient for a minimum of 24 hours and it records the patient's blood pressure every 30 minutes of the patient's waking day. The idea behind this is to rule out any 'white coat syndrome' and to get a range of readings as the patient goes about their usual day to day activities. In this way, when the readings are analysed (an average of at least 14 readings are taken by the clinician), it confirms diagnosis immediately and treatment can be initiated^{1,3}.

The value of repeated measurements in different settings has been shown in evidence from as early as the 1970s^{2,5}. Research has also shown that patients usually have a high blood pressure reading initially which drops after subsequent measurements, hence the new guidelines are in place to allow for a range of readings before diagnosing and treating hypertension^{1,3}.

Investigations

While the patient is still in the clinic, assess the patient's overall cardiovascular risk score using the cardiovascular risk assessment tool³. Perform a thorough physical examination, including looking for evidence of target organ damage, for example, left ventricular hypertrophy, renal disease, peripheral vascular disease and changes in the retina from raised blood pressure^{1,3,5}. If there is suspicion of hypertension, send the patient home on an ABPM³. While waiting for the results of the ABPM, any patient under investigation for hypertension needs to have a baseline set of tests^{1,7-8}. This includes a full blood count, renal function tests, liver function tests, a fasting glucose and cholesterol blood test, an ECG (electrocardiogram) and a urine dip. These tests are a basic screen for assessment of target organ damage^{6,9}. If these investigations are not adequate, a patient can be referred for more extensive investigation for target organ damage, for example, an echocardiogram or a renal ultrasound/angiography^{1,3,5}.

Any patient that is young or presenting with persistent hypertension, especially that which does not respond to treatment, needs further investigation for other causes, such as renal disease, adrenal disease, alcoholism or steroid use (not to forget the oral contraceptive pill can also cause hypertension^{1,7,9}).

In general, a patient should be treated if their blood pressure readings are persistently 140/90mmHg or higher. For those that have borderline readings, for example, 135/85mmHg, clinicians must assess their cardiovascular risk score and look for target organ damage. If there is evidence for either of these, a patient should be started on treatment immediately¹.

Treatment

Non-pharmacological

First line treatment of hypertension is always non-pharmaceutical; also known as 'lifestyle changes'^{1,3,5,9}. Attempt to find out the details of the patient's diet, weight, employment, stress levels at work/home, exercise, alcohol intake and smoking habits. Once established, assist the patient in altering their lifestyle choices in order to lower their blood pressure. Patients often feel overwhelmed and many benefit from group activities, such as smoking cessation and weight loss groups³. Other ideas include a dietician referral, counsellors if they are struggling with motivation and low moods, gym sessions/personal trainers. Encourage the patient in that if they succeed in altering their lifestyle and therefore bringing down their blood pressure, they can avoid prescription medication.

Lifestyle changes can delay hypertension for many years but if the blood pressure continues to creep upwards in subsequent multiple visits and lifestyle options have been exhausted, it would then be appropriate to start pharmacological management^{1,3,5}.

Pharmacological Treatment

In general terms, always start with monotherapy and increase the dose according to patient response. According to NICE guidelines from 2011, if a patient is over 55 years of age and/or Afro-Caribbean in origin, start with a calcium channel blocker, such as Amlodipine³. If these are contra-indicated, start with a thiazide diuretic³. In regards to thiazide diuretics, the new NICE guidelines state that Chlortalidone (12.5–25.0 mg once daily) or Indapamide (1.5 mg modified-release or 2.5 mg once daily) should be used in preference to what clinicians have been prescribing for years, namely Bendroflumethiazide and Hydrochlorothiazide³. For those who are already on these conventional thiazide diuretics, NICE state that if the patient's blood pressure is stable, to continue with Bendroflumethiazide or Hydrochlorothiazide³.

Patients diagnosed with hypertension who are under 55 years of age, should be started on an ACE inhibitor (Angiotensin Converting Enzyme inhibitor), for example, Ramipril³, but if

this is not tolerated, replace it with an ARB (Angiotensin II Receptor Blocker) such as Losartan³.

Review the patient every few weeks initially and extend the reviews to 6 months once the blood pressure is within therapeutic range⁶. Do not forget to check the patient's renal function in the first few months of starting a new drug and always be aware that if a patient's blood pressure drops drastically after starting an ACE inhibitor this suggests underlying renal disease and must be investigated^{1,3,5,9}.

Continue to titrate the dose of the drug until the patient's blood pressure is satisfactory. Consider adding in a second agent when the patient is nearing maximum dose of the first agent and the blood pressure is rising again^{3,5}. Depending on what the patient is on, add in either an ACE inhibitor, ARB or a calcium channel blocker, for example, if patient is on Ramipril, add in Amlodipine and vice versa³. If a calcium channel blocker is not tolerated as second line, consider using thiazide diuretics. Afro-Caribbean patients who are already on calcium channel blockers, add in an ARB, rather than an ACE inhibitor³.

Following that, if the blood pressure is still not within therapeutic range, consider adding in a third agent or alternatively, discontinue the first agent and continue with the second and add a third from among an ACE inhibitor, ARB or calcium channel blocker. Consider a thiazide diuretic if patients are intolerable to any of the above³.

Beta-blockers should not be considered in treating hypertension, according to NICE, unless the patients are very young or intolerant to ACE inhibitors, ARBs or calcium channel blockers³.

Beware and monitor closely any elderly patients who are on antihypertensives as the physiology of ageing interferes with the drugs, for example, decreased clearance of drugs from the kidney or liver, decreased sensitivity to baroreceptors (postural hypotension), chronic sodium retention and reduced cardiac reserve. Do not forget communication and compliance issues with the elderly also^{1,7}.

Make sure there is an annual review for each patient that has been diagnosed with hypertension in order to get blood pressure readings, medication review and how the patient is coping with lifestyle changes or side effects of the antihypertensives.

When to Refer

Resistant hypertension is defined as a patient remaining hypertensive despite being on triple or quadruple drug therapy^{3,7}. Consider starting a low dose of Spironolactone (if the serum potassium is less than 4.5mmol/l) and refer to a specialist for advice^{3,4}.

If subsequent readings are 180/110mmHg or more, start antihypertensives immediately and refer the patient to hospital.

Also refer immediately if retinal haemorrhages or papilloedema are seen^{1,3}.

Summary

If a patient is suspected to have hypertension, send them home with an ABPM and perform baseline tests^{1,3}.

Start treatment if blood pressure is 140/90mmHg and ABPM average is 135/85mmHg and/or patient has one of the following:

- target organ damage
- established cardiovascular disease
- renal disease
- diabetes
- 10-year cardiovascular risk equivalent to 20% or greater (NICE guidelines, 2011)³

Start on monotherapy and review every few months, until blood pressure is stable³.

Review yearly after stability has been reached and consider adding in further antihypertensives if the blood pressure rises again.

Book patients in for annual reviews of end organ damage as this is an excellent overview of disease progression.

Hypertension is to be respected in light of its incredible contributor to morbidity and mortality. Never underestimate the importance of keeping a patient's blood pressure within the desired range⁴.

Competing Interests

None declared

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Co-incident finding of pancytopenia

W Thomas and M Beveridge

ABSTRACT

A 73 year old man was found to be pancytopenic after visiting his General Practitioner for a routine health check. He had a history of spinal bulbar atrophy and hypertension. In this teaching case we discuss the investigation and immediate management of the patient, with the outcome of the case also being revealed. The case is an educational piece intended to be at the level required of candidates preparing to sit the membership of the Royal College of Physicians of the United Kingdom.

KEYWORDS: pancytopenia, differential diagnosis.

CASE REPORT

A 73 year old male retired civil servant with a background of spinal bulbar atrophy and hypertension presented to his General Practitioner (GP) for a routine health check. He was taking bendroflumethiazide, propranolol, atorvastatin and aspirin. His brother also has spinal bulbar atrophy.

The GP sent routine blood tests, which came back as follows: Haemoglobin 8.5 (13-17g/dL), Mean Cell Volume 84.9 (80-100fl), White Cell Count 3.4 (4-11 $\times 10^9/L$), Neutrophil Count 0.68 (2-8 $\times 10^9/L$), Platelets 19 (150-400 $\times 10^9/L$). A random blood sugar reading was 18 (3.9-7.8mmol/L). Renal function, bone profile and hepatic function tests were normal. The General Practitioner referred the patient urgently to the local Haematology unit for further assessment.

On further review the patient complained of tiredness but had had no infections or bleeding. There were no night sweats or recent foreign travel. Physical examination was unremarkable, with no lymphadenopathy or organomegaly.

A blood film showed marked anaemia with red cell anisopoikilocytosis, prominent tear drop cells and neutropenia with normal white cell morphology. There were no platelet clumps. A diagnostic investigation followed.

QUESTIONS

What are the differential diagnoses of pancytopenia and which causes are likely here given the findings on examination of the peripheral blood film?

Infections - Viral infections including cytomegalovirus, hepatitis A-E, Epstein-Barr virus, Parvovirus B19 and non A-E hepatitis viruses can cause aplastic anaemia¹. The classical

picture would be pancytopenia in a young patient who has recently had 'slapped cheek syndrome' from parvovirus B19 who has transient bone marrow aplasia. Tropical infections such as visceral leishmania may cause pancytopenia, splenomegaly and a polyclonal rise in immunoglobulins². Overwhelming sepsis may also cause pancytopenia with a leucoerythroblastic blood film (myeloid precursors, nucleated red blood cells and tear drop red cells). HIV is also an important cause of cytopenias.

Medications - common medications may cause aplastic anaemia, such as chloramphenicol, azathioprine and sodium valproate. The history in this case did not have any recent medications introduced. The other very common cause of pancytopenia in modern practice would be in the context of chemotherapy.

Bone marrow disorders - tear drop cells are a key finding and clue in this case. They suggest an underlying bone marrow disorder and stress. In the context of a known active malignancy they are nearly indicative of bony metastases. Our patient did not have a known malignancy and there was nothing to suggest this on the history or physical examination, although in a man of this age metastatic prostate cancer should be considered. Other bone marrow disorders that would need to be considered are acute leukaemia (which was the diagnosis here), myelodysplasia and myelofibrosis. Splenomegaly would be especially significant in this case as it would be highly suggestive of myelofibrosis in combination with tear drop cells with pancytopenia in an elderly patient³.

B12 and folate deficiency - this may cause pancytopenia, tear drop cells and leucoerythroblastic blood findings^{4&5}. The mean corpuscular volume in this case however is normal which would somewhat argue against B12 and folate deficiency, as

well as the fact that there were no hypersegmented neutrophils seen on the blood film. This cause is however very important given how it is easily reversible and treatable.

Haemophagocytosis – this is a bone marrow manifestation of severe inflammation and is a manifestation of systemic disease⁶. It has various causes including viruses (e.g. Epstein Barr virus), malignancy and autoimmune disease. It should be considered in patients with prolonged fever, splenomegaly and cytopenias. It is diagnosed by characteristic findings on bone marrow biopsy.

Paroxysmal nocturnal haemoglobinuria – this is a triad of pancytopenia, thrombosis and haemolysis caused by a clonal stem cell disorder with loss of membrane proteins (e.g. CD55 and CD59) that prevent complement activation⁷.

Genetic disease – Fanconi anaemia is a rare autosomal recessive disease with progressive pancytopenia, malignancy and developmental delay. It is caused by defects in DNA repair genes.

The key finding in this case was tear drop cells on the blood film. These are part of a leucoerythroblastic blood picture seen in bone marrow disease, malignant marrow infiltration, systemic illness and occasionally haematinic deficiency. See above for why this is unlikely to be haematinic deficiency. Although tear drop cells can occur in systemic illness such as severe infection, the history here was not in keeping with this. The diagnoses remaining therefore are malignant bone marrow infiltration or a primary bone marrow disorder (myelodysplasia, acute leukaemia or myelofibrosis). There were no features in the history pointing towards a metastatic malignancy and therefore primary bone marrow disorder is the most likely diagnosis. The diagnosis was later established as acute myeloid leukaemia on bone marrow examination.

What investigations would help to confirm or eliminate the possible diagnoses?

Blood tests including a clotting screen, liver function tests, inflammatory markers and renal function shall help to exclude other systemic disease such as disseminated intravascular coagulation, sepsis, liver disease and thrombotic thrombocytopenic purpura which may all give rise to cytopenias. Autoimmune screening may also suggest vasculitis which can cause cytopenias.

Microbiology studies including virology tests (e.g. human immunodeficiency virus, Epstein Barr virus and hepatitis viruses) may also be requested as appropriate given the clinical scenario and findings. Visceral leishmania should be tested for according to travel history and clinical likelihood. Leishmania may be identified through serology and light microscopy (for amastigotes) or polymerase chain reaction of the bone marrow aspirate. Tuberculosis could be cultured from the bone marrow if suspected.

Haematinics are a crucial test and the aim should be to try and withhold transfusion until these results are known in case they can easily be replaced thereby negating the need for blood products. Remember that if haematinics are not tested before transfusion then the blood products will confound the tests results.

Bone marrow biopsy, including aspirate and trephine are a crucial investigation for morphological examination and microbiological testing if indicated. This will distinguish the bone marrow disorders including acute leukaemia, myelofibrosis, bone marrow metastatic infiltration and myelodysplasia. Haemophagocytic syndrome may also be suggested by bone marrow examination findings.

Imaging if there is suspicion of an underlying malignancy (e.g. CT chest, abdomen and pelvis) and then further blood tests such as the prostate specific antigen. Ultrasound could also be used to check for splenomegaly where clinical examination has not been conclusive.

Medication review is vital as this may reveal the diagnosis (e.g. use of chloramphenicol)

Flow cytometry may be considered to investigate for an abnormal clone in the case of paroxysmal nocturnal haemoglobinuria and may be used on bone marrow samples to further evaluate the cells.

Unless a very clear cause for the pancytopenia is obvious (e.g. haematinic deficiency or malignant infiltration) then bone marrow examination is crucial for establishing a diagnosis. This will also prevent inappropriate treatments being initiated.

What immediate management steps and advice would be given to this patient?

General measures for pancytopenia include blood product support. Red cells and platelets can be given for symptomatic anaemia and bleeding. There is no need to transfuse platelets in the patient if there are no signs of bleeding. Alternatively he could also be treated with tranexamic acid as an alternative to avoiding risks associated with platelet transfusion. Infection should be treated urgently. Due to the neutropenia he should be advised to seek medical help if he develops a fever or sore throat. He should urgently be followed up in clinic with the results and given the contact details for the haematology department in the interim period in case he develops any problems.

The specific treatments for pancytopenia rests on the exact cause found after investigation. In this case the diagnosis was acute myeloid leukaemia arising from a background of myelodysplasia. The treatment for acute myeloid leukaemia in general, with curative intent, would consist of induction chemotherapy with DA (daunorubicin and cytosine arabinoside) followed by consolidation with further

chemotherapy, the type of which (e.g. high dose cytosine arabinoside or FLAG-Ida) would depend on the risk assessment of the disease and possible consideration of an allograft bone marrow transplant after consolidation. Currently different approaches to consolidation chemotherapy, transplantation and small molecule inhibitors are being evaluated in clinical trial (e.g. AML 17 clinical trial).

The other options, in older more frail patients where high dose chemotherapy will be very toxic, are low dose palliative chemotherapy and support with transfusion.

PATIENT OUTCOME

He has been supported with blood products (platelets and packed red cells for bleeding and anaemia respectively). After discussion with him and his wife he has elected to have palliative chemotherapy with low dose cytosine arabinoside. He will be seen regularly in the haematology clinic and day unit for review. We do not suspect a link between the leukaemia and spinal bulbar atrophy.

Competing Interests

None declared

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