Diagnosing and managing iron deficiency anaemia in adults

A practical, clinical approach to iron deficiency anaemia.

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Uncomplicated iron deficiency anaemia (IDA) is usually easy to diagnose and treat. However, most of us have been faced at times with uninterpretable iron studies or an inexplicable failure of patients to respond to therapy. The aim of this article, therefore, is not to be comprehensive but rather to provide a practical, clinical approach with particular comment on common dilemmas experienced in diagnosing and managing IDA. Some understanding of iron physiology is very helpful in interpreting iron studies and I have included this where relevant.

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Clinical features

IDA may present with any of the nonspecific symptoms of anaemia, including lethargy, reduced effort tolerance and depression. If it develops slowly, adaptive mechanisms may allow the patient to tolerate extremely low levels of haemoglobin with relatively few symptoms. Interestingly, however, lethargy is often a far more prominent feature in IDA than in anaemia of equivalent severity due to other causes. Iron deficiency, even in the absence of anaemia, can cause significant fatigue and reduced effort tolerance, which respond to iron replacement. This reflects the impaired function of iron-containing enzymes and proteins other than haemoglobin. Iron deficiency can also impair cognitive function and cause headaches, irritability, tinnitus and taste disturbances. It should not be forgotten when investigating these symptoms. Deficiency of iron in epithelial cells not infrequently causes glossitis, burning of the tongue, angular stomatitis and dry, itchy skin. However, the more classic symptoms such as oesophageal webs and koilonychia (ridging, splitting and spoon-like concavity of the nails) are extremely rare. Pica – a craving to eat unusual (usually gritty) substances such as sand, ice or even matches – is a very specific symptom. The sale of bags of sand to commuters at taxi ranks in central Johannesburg is a good indication of how prevalent IDA is in South Africa!

Diagnosis

Investigation of a patient suspected of having IDA involves identification of the cause and assessment of iron status.

Iron deficiency may be due to reduced iron intake because of dietary deficiency or malabsorption or to an increased demand because of haemorrhage or increased physiological requirements, e.g. in pregnancy.

Identifying the cause

Iron deficiency may be due to reduced iron intake because of dietary deficiency or malabsorption or to an increased demand because of haemorrhage or increased physiological requirements, e.g. in pregnancy. The cause is often clear after a thorough history and clinical examination. However, in the absence of any obvious cause a full gastrointestinal (GIT) work-up is mandatory, particularly in men and postmenopausal women. Younger women and adolescents refractory to optimal oral therapy should also be thoroughly investigated. If gastroscopy and colonoscopy are unhelpful, these investigations should be followed by capsule endoscopy if ongoing GIT blood loss is suspected. It is also now recognised that as many as 20 - 30% of patients with IDA may suffer from some form of chronic malabsorption, e.g. caused by coeliac disease or autoimmune gastritis, even in the absence of GIT symptoms. Simple non-invasive tests for these conditions including assessment of anti-endomysial IgA antibodies, tissue transglutaminase, serum gastrin, and anti-parietal cell antibodies, and (more controversially) a *Helicobacter pylori* breath test should therefore be considered in appropriate cases.[1] This will be covered in the article by Dr Barrow (pg. 246 of this issue).

Assessment of iron status

In clinical practice, the initial screening for IDA almost invariably includes measuring the haemoglobin level or the haematocrit. Red

cell indices including mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) may confirm the presence of a microcytic hypochromic anaemia. However, the MCV is one of the last parameters to change in the presence of iron deficient erythropoiesis and is only consistently abnormal in an adult in the presence of a moderate to severe anaemia.[2] Examination of the peripheral smear is equally insensitive and the classic features of this smear (hypochromic microcytic red cells, target and pencil cells – see Fig. 1) are only obvious in severe IDA. An important pitfall to avoid is to regard all microcytic anaemia as being IDA. Patients with thalassaemia have a marked microcytosis but often have iron overload because of their chronic anaemia; consequently the reflex prescribing of iron supplements is harmful. It is therefore essential to proceed to iron studies in order to assess iron status.

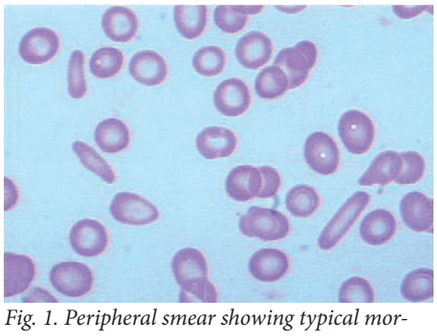

Fig. 1. Peripheral smear showing typical morphological changes associated with IDA (hyperchromic microcytic red cells with central pallor, target cells and pencil poikilocytes).

Traditionally, iron studies include serum iron, ferritin, transferrin and percentage saturation. Despite common usage, serum iron *per se* is not a reliable indicator of iron status and the combined assessment of serum ferritin and transferrin probably provides the best guide. Some understanding of iron physiology helps to explain this. Free iron is toxic and iron is always protein bound under physiological conditions. The two major iron-binding proteins are ferritin – the major storage protein – and transferrin – the principal iron transport protein. Serum ferritin levels are in equilibrium with intracellular iron stores and would probably be the best indication of iron status, except that ferritin is an acute-phase reactant and levels can be significantly increased in the absence of iron overload. Measurement of serum ferritin alone is therefore not reliable and it needs to be interpreted in conjunction with transferrin. These two proteins are reciprocally regulated.[3] In low iron conditions transferrin synthesis is increased to try to maximise iron absorption and transport while ferritin synthesis is reduced. In high iron states the opposite occurs with downregulation of transferrin synthesis and increased synthesis of ferritin. High ferritin

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levels in the presence of low transferrin levels are therefore indicative of iron overload, while low (or low normal) ferritin levels in the presence of high transferrin levels would be indicative of iron deficiency. Should there be discordance between the two parameters, the possibility of complicating factors such as an acute-phase ferritin response would have to be considered.

The two other components of traditional iron studies often cause more confusion than clarity. Serum iron levels merely reflect the amount of circulating iron bound to transferrin. This is affected by numerous factors including diurnal variation and timing of the latest iron-containing meal! Patients who have fasted overnight for cholesterol or glucose studies done simultaneously are therefore likely to have low serum iron levels. Percentage saturation is the proportion of transferrin carrying bound iron. It is more valuable in the diagnosis of haemolysis and haemochromatosis (when significant elevation can occur) than in the diagnosis of iron deficiency. This is because, as with serum iron, low levels can be due to various factors including the presence of high levels of hepcidin.

Hepcidin plays an essential role in the regulation of iron transport.[4] The majority of iron utilised for haem synthesis is derived from degradation of senescent red cells in the macrophages. Small amounts of iron are also derived from dietary iron absorbed via GIT enterocytes. The exit of iron from either the macrophages or enterocytes into the circulation to allow transport to the marrow for erythropoiesis, is largely dependent on a molecule called ferroportin. Hepcidin blocks the exit of iron from cells by binding to ferroportin and inducing internalisation and degradation of this molecule. It is synthesised in the liver in response to iron overload and in inflammatory states, and in these conditions iron becomes trapped within cells. (This is the basis of reticulo-endothelial iron blockade in an anaemia of chronic disorders (ACD).[5]) This results in low serum iron and low percentage saturation, which do not necessarily reflect iron deficiency. In contrast, the presence of anaemia or hypoxia as well as iron deficiency results in inhibition of hepcidin synthesis, allowing rapid exit of iron from cells and transport to sites where it can be utilised. This may result in higher serum iron and percentage saturation levels than would be expected in a patient with iron deficiency, particularly if a recent iron load has been given.

Various other assays have been used but are not routinely available. One worth mentioning is the soluble transferrin receptor (sTfR)[6] which can help to distinguish between IDA and ACD. Circulating transferrin-bound iron enters cells via a transferrin receptor. There the iron is released and the transferrin returns to the circulation in what is known as the transferrin cycle. The density of expression of transferrin receptors is proportional to the cells' iron requirements. Not surprisingly they are most densely expressed on red cells and are markedly increased in iron deficiency. sTfR is in equilibrium with the amount of surface transferrin receptor and is a good measure of the iron 'hunger' of the red cells, but problems with standardisation of the assay have limited its use.

Bone marrow aspiration, previously considered to be the gold standard, is not indicated in routine practice. It is painful, expensive, subjective and dependent on the quality of the aspirate and should be reserved for cases where there is a real diagnostic dilemma[7] (summarised in Table I).

Management of IDA

Effective management of IDA relies on both appropriate management of the underlying cause and iron replacement therapy.[8]

Iron replacement therapy

Inorganic iron from plant sources is poorly absorbed and its absorption can be blocked by various iron binders including tannins from tea and phytates in cereals (and spinach!). Impractically large quantities are therefore required if this is the only dietary source. In contrast, haem from animal proteins is efficiently absorbed and less subject to dietary interference. Red meat is the most effective dietary source of iron for replacement therapy. In addition, only a limited amount of iron can be absorbed at any one time and it is of more value to eat small amounts of red meat frequently than an occasional large portion of meat. Iron supplements should be given in divided doses for the same reason. As with inorganic dietary iron, absorption is influenced by the oxidation state and the presence of dietary iron binders and can be improved by adding

vitamin C (a reducing agent) and avoiding concomitant use of iron binders. A classic mistake is to take 2 or 3 iron tablets in the morning with tea and cereal, resulting in very limited absorption! In many patients, apparent refractory IDA can be resolved merely by adjusting the way the iron tablets are taken. GIT side-effects of oral iron supplements are a problem.[9] These range from dose-related nausea and epigastric discomfort to diarrhoea and constipation, which are usually not dose related and are sometimes difficult to manage. Supplements comprising inorganic iron (ferrous sulphate or ferrous gluconate) are best absorbed on an empty stomach. However, this can aggravate GIT side-effects. Iron polymaltose complexes are best tolerated and absorbed and do not suffer from the same interference with other dietary components.

Commercial iron preparations promoted on the basis of fewer side-effects are often less well absorbed or contain much smaller amounts of elemental iron. Ideally, a dose of between 50 mg and 100 mg of elemental iron should be given twice a day, and it is important to check the amount of elemental iron present in the preparation selected. Concomitant use of folic acid can also improve response. It is well recognised that at times of increased haemopoietic demand, folic acid supplementation is indicated, but for some reason this is often forgotten when initiating treatment with iron in patients who are significantly anaemic.

Table I. Assessment of iron status

Parameter	Comment
• ↓ Hb	Symptomatic iron deficiency may be persent first
• ↓ MCV	One of the last parameters to change
• Ferritin ↓	Good measure of iron stores but also an acute phase reactant
• Transferrin ↑	Helpful in interpreting ferritin level
• ↓ serum iron • ↓ % saturation	Not reliable – affected by diet, diurnal variation and hepcidin levels
• ↑ sTfR	Good measure of tissue iron deficiency but problems with assay
• Bone marrow aspirate	Not indicated

Table II. Oral iron absorption test

- Patient to fast overnight
- Sample taken for baseline iron studies
- Serum iron measured at 30 min, 1, 2 and 3 hours after the dose
- Either:
  - 300 mg oral iron administered in liquid form
  - <3-fold increase in serum iron over baseline indicates malabsorption
- Or:
  - 60 mg ferrous sulphate administered
  - Increase in serum iron <100 µg/dl over baseline indicates maladsorption

Table III. Intravenous administration of iron sucrose

- Maximum daily dose – 300 mg
- Dose interval from 24 hours
- Dilute in 100 ml normal saline and infuse over 15 min (reduces risk of hypotension)
- No test dose required
- Assess response after minimum of 7 days (sucrose interferes with assay)

Monitoring response to therapy

Effective iron replacement should result in an increase in haemoglobin levels of approximately 1 g/dℓ per week. Changes in the red cell distribution width and a reticulocyte response can often be detected much earlier. Once haemoglobin is within the normal range, iron replacement should be continued for a further 3 months to replenish stores. Failure to respond to oral iron therapy is usually due to poor compliance but may also occur if there is ongoing loss (bleeding) exceeding the amount of iron absorbed daily, malabsorption of iron caused by non-bleeding GIT conditions, or inflammatory states associated with increased hepcidin levels.

Iron absorption tests

Iron absorption or 'tolerance' tests involve giving the patient an oral dose of an inorganic iron compound and monitoring subsequent changes in serum iron concentration (Table II).[10] An appropriate increase in serum iron should indicate normal absorption. However, this does not always correlate with good clinical response. This may be due to non-compliance but in some cases other factors may alter the internal flow of iron. In either scenario alternative therapy is usually required and the test does not alter subsequent management. It is therefore of limited practical value, and although first described in the 1960s it is not widely used.

Management of refractory IDA

Intravenous therapy is indicated in patients who remain refractory despite optimal oral iron replacement.[7,11] Newer intravenous preparations do not carry the same risk of severe anaphylaxis and are indicated for patients intolerant of oral iron, patients with losses exceeding the potential for oral absorption, those with inflammatory conditions, including inflammatory bowel disease causing iron malabsorption, and patients in whom a particularly rapid response is desirable, e.g. those with severe anaemia in late pregnancy. These products should not be given intramuscularly. All preparations contain an iron-oxyhydroxide core with a carbohydrate shell comprising sucrose, dextrose or gluconate. Differences in the carbohydrate shell give rise to different pharmacokinetic properties and safety profiles. Side-effects may include hypotension, cramping, muscle pain and sometimes diarrhoea. The risk of anaphylaxis appears to be limited to iron dextrose preparations, possibly because of induction of mast cell degranulation by the dextrin polymers. Iron sucrose is the safest preparation and has never been associated with a fatality. Practical aspects regarding its use are outlined in Table III.

Final comments

Although iron deficiency is the commonest cause of anaemia, it is important to evaluate adult patients properly to determine the cause and assess iron status before giving iron supplements. The majority of patients will respond rapidly to optimised oral iron supplementation. For those who do not, current intravenous iron preparations are safe and efficient.

References

1. Annabale B, Capuso G, Christolini A, *et al.* Gastrointestinal causes of refractory iron deficiency anaemia in patients without gastrointestinal symptoms. *Am J Med* 2001; 111: 439-445.
2. Beutler E. The red cell indices in the diagnosis of iron deficiency anaemia. *Ann Int Med* 1959; 50: 313.

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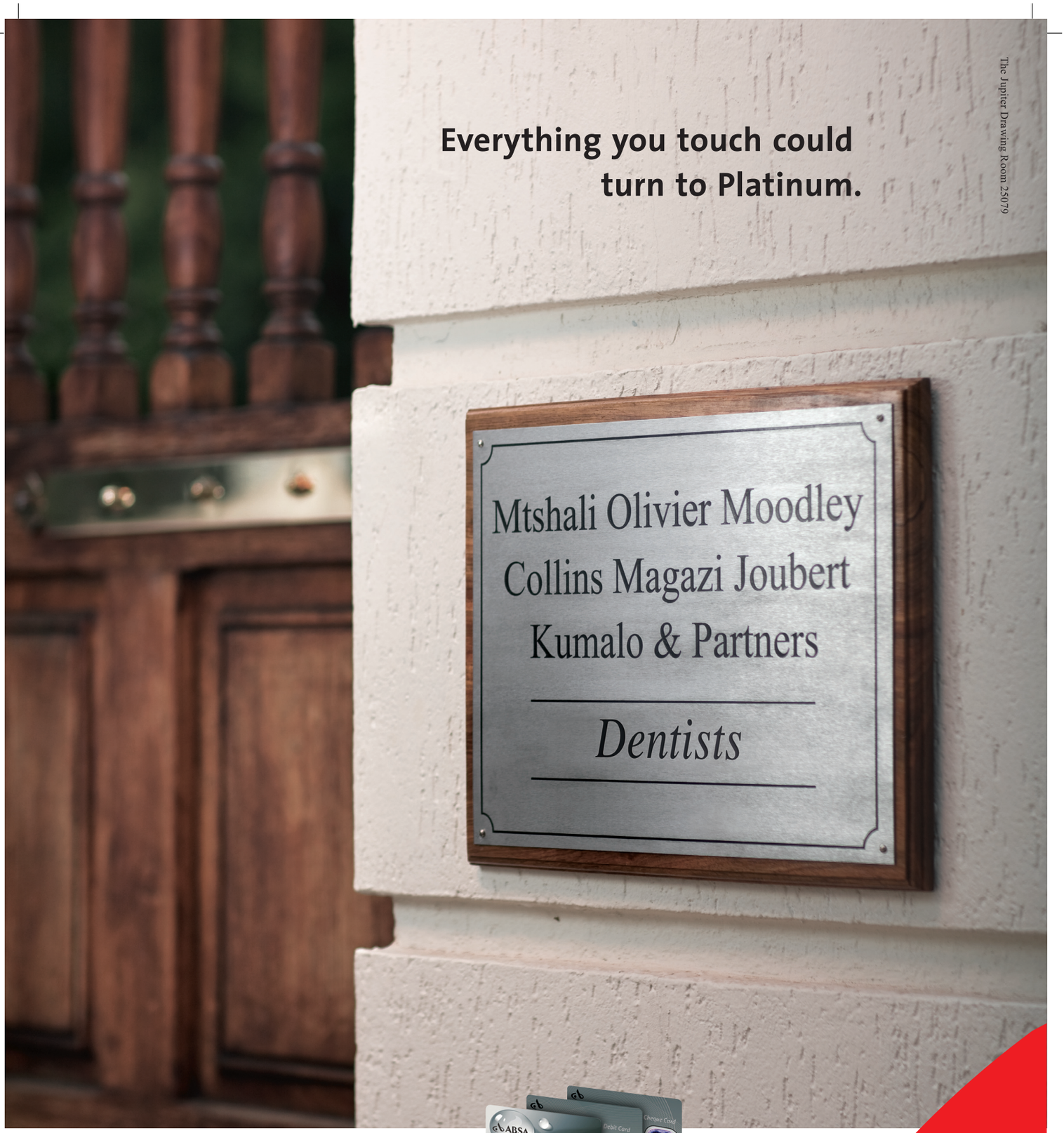

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3. Hentze MW, Muckenthaler MU, Andrews NC. Balancing acts. Molecular control of mammalian iron metabolism. *Cell* 2004; 117: 285-297.
4. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anaemia of inflammation. *Blood* 2003; 102: 783-788.
5. Weiss G, Goodnough LT. Anaemia of chronic disease. *N Engl J Med* 2005; 352: 1011-1023.
6. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. *Blood* 2003; 101: 3359-3363.
7. Cook JD. Newer aspects of the diagnosis and treatment of iron deficiency. *Haematology.* San Diego, Calif: American Society of Haematology Educational Program Book, 2003: 53-61.
8. Provan D. Mechanisms and management of iron deficiency anaemia. *Br J Haematol* 1999; 105: 19-26.
9. Cook JD. Diagnosis and management of iron deficiency anaemia. *Best Pract Res Clin Haematol* 2005; 18(2): 319-332.
10. Hauge BN. The iron absorption test: Clinical investigation and evaluation. *Acta Med Scand* 1960; 168: 109.
11. Grau PW. Intravenous iron therapy. Disorders of haemostasis, erythrocytes, erythropoieisis. *European School of Haematology Handbook*. Genoa, Italy: Forum Service Editore, 2006: 421-434.

In a nutshell

- Iron deficiency can cause symptoms, even in the absence of anaemia.
- Microcytosis is a late manifestation of iron-deficient erythropoiesis.
- Raised serum ferritin in conjunction with low serum transferrin provides the best indication of iron deficiency.
- Serum iron and percentage saturation are poor indicators of iron status.
- Investigation of iron deficiency must include identification of the cause.
- Simple non-invasive tests are available to exclude disorders of the GIT associated with malabsorption which may be present, even in the absence of GIT symptoms.
- Management should begin with optimisation of oral iron intake.
- Polymaltose iron preparations are generally better tolerated and should be given in divided doses in the absence of dietary iron binders such as phytates in cereal. Concomitant vitamin C and folate supplementation may enhance response.
- Failure to respond may be due to non-compliance, excessive loss or malabsorption due to GIT pathology or chronic inflammatory states.
- Newer intravenous iron preparations are safe and effective and are indicated in patients refractory to optimised oral therapy.

Single Suture

Paroxetine and suicide risk

Court documents released in January this year suggest that GlaxoSmithKline withheld trial data that showed an increased risk of suicide associated with the use of paroxetine for 15 years. It was not until 2006 that GSK alerted people to the increased suicide risk associated with the use of this drug. It appears that the company had trial data showing an eightfold increase in suicide risk as early as 1989.

There are currently around 30 cases being brought against GSK in the USA, linking suicides and suicide attempts to the use of paroxetine. The analysis of the trial data focuses on the 'washout' phase before a trial starts, during which subjects stop taking all or most other medications to avoid confusion with results from the trial itself. Because the washout happens before patients randomly receive either the drug or a placebo, adverse events during this time cannot be attributed to the trial and so are seldom, if ever, included in the results. But GSK researchers who submitted data on paroxetine to the US Food and Drug Administration in the late 1980s and early 1990s included suicides and suicide attempts from the washout period in the results from the placebo arm of the trial, but not from the paroxetine arms. It is possible that if the washout results had been excluded, the results would have shown an eightfold risk of suicidal behaviour in adults.

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