

# ALLERGIC RHINITIS PRESCRIPTION – WHERE TO NOW IN SOUTH AFRICA?

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## ABSTRACT

This article is a retrospective review of the sales data of medications (both over-the-counter (OTC) and prescribed), relating to current legislative changes as well as cost pressures in South Africa. The results tend to suggest that older first-generation antihistamines are being increasingly used, mainly on a perceived cost basis, disregarding published prescribing and safety information. There may not even be a cost benefit to this prescription. Despite all the ongoing education, the problem exists at OTC, pharmacy and prescriber levels.

'Doctor, I have sinus'. These words are heard many times daily in ENT and allergist consultations. Critical evaluation of the developing face of antihistamine prescription, including the influences of state-influenced mandatory substitution, pharmacy over-the-counter (OTC) medication and therapeutic substitution, as well as all the managed care offensives we are subjected to, clearly points to a major problem. The funders and their managed care partners appear to be driving this problem in their own interests and the medical profession is ignorant or just does not care. The public at this stage is totally in the dark.

In 2002 in the USA there was a massive move by pharmaceutical companies to raise the product prices in advance of moves by regulators to regulate and enforce generic substitution – they appeared to understand the problem.

## ALLERGIC RHINITIS

Allergic rhinitis is a common, significant condition affecting all ages. Whereas its symptoms and their effects are well known, what are often not given enough importance, are its economic implications. Pharmaceutical companies, managed care organisations and funders are very sensitive to this. Compounding this is the fact that suboptimal treatment, or no treatment at all, results in such significant comorbidities that quality of life and compromised productivity at work and school is enormous.<sup>1</sup>

Only immunotherapy has a chance of sustained control of allergic rhinitis. On the other hand we have very good medications that are capable of

excellent disease process control. These are proven medications that have stood the test of time, but they require good scripting, pharmacy compliance and patient education and compliance.

Despite all the continuing medical education, publicity around the ARIA document,<sup>2</sup> package insert warnings and common sense, inappropriate prescription for allergic rhinitis appears to be the rule.

Allergic rhinitis is a common and often trivialised disease. More than 50% of USA citizens test positive for one or more allergens<sup>3</sup> and allergies are the sixth leading cause of chronic disease.<sup>10</sup> Most sufferers would be subject to the same choice of medications.

With nasal allergy an increasing complaint, and up to 20% of patients with nasal allergy having chronic sinusitis as a comorbidity,<sup>3</sup> this problem is further compounded. In addition, other comorbidities of otitis media with effusion, allergies and sleep apnoea make the size of this prescription problem more apparent. To make the scenario more graphic, the majority of previously untreated (uncounselled) patients with nasal symptoms of any sort, in particular nasal obstruction, feel they have a disease called 'sinus'.

## PRESCRIPTION PATTERNS

The prescription patterns of the groups of drugs used (OTC & prescribed) illustrates the size of this prescription problem (Fig. 1). The South African population is approximately one-sixth that of the USA for comparison purposes. Approximately 7 million lives are covered by private health insurance.

Studies have tended to agree with the hypothesis that the dominant treatment for allergies is OTC medications, all of which have sedating side-effects that may pose safety and productivity concerns.<sup>4</sup>

## DATA

### Nasal medications

Categorisation of medications per group are shown in the addendum.

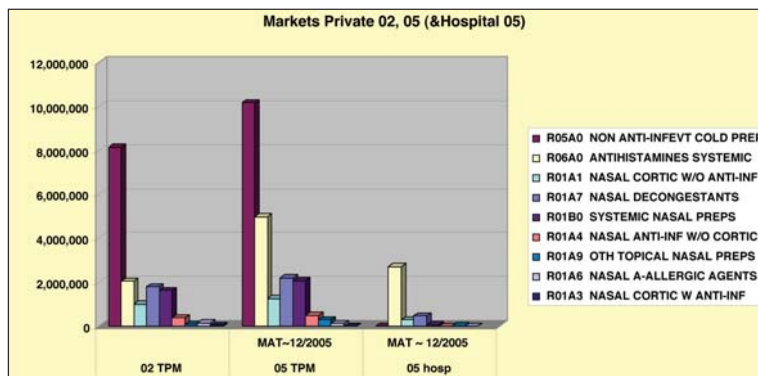


Fig. 1. Unit sales 'Nasal medications' (see addendum).

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If we break down the group R05A0 (Figs 2 and 3), most allergy specialists will recognise the problem drugs.

The unit numbers and the South African Rand value (ZAR) numbers almost parallel each other in this group

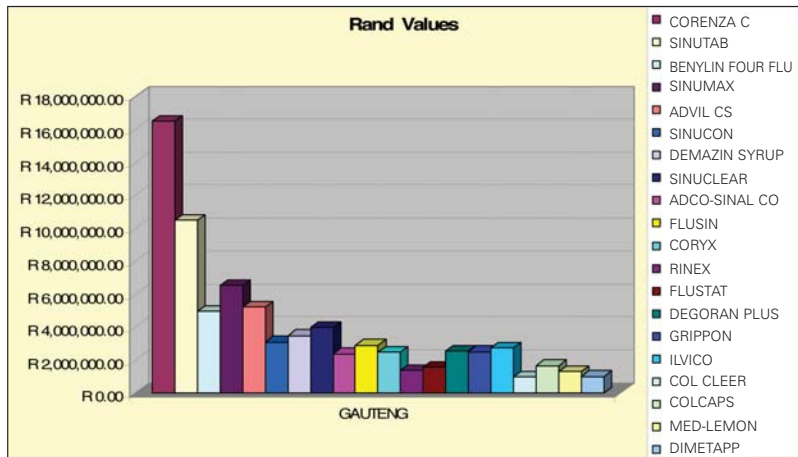


Fig. 2. R05A0 Rand value.

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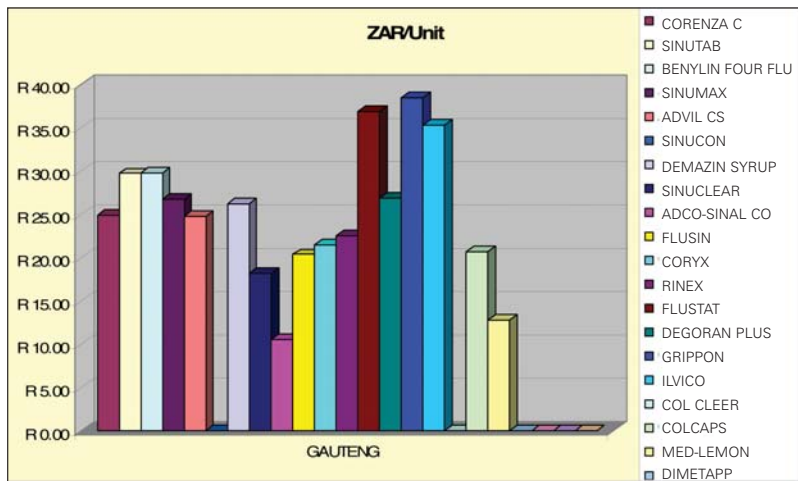


Fig. 3. R05A0 ZAR/unit value.

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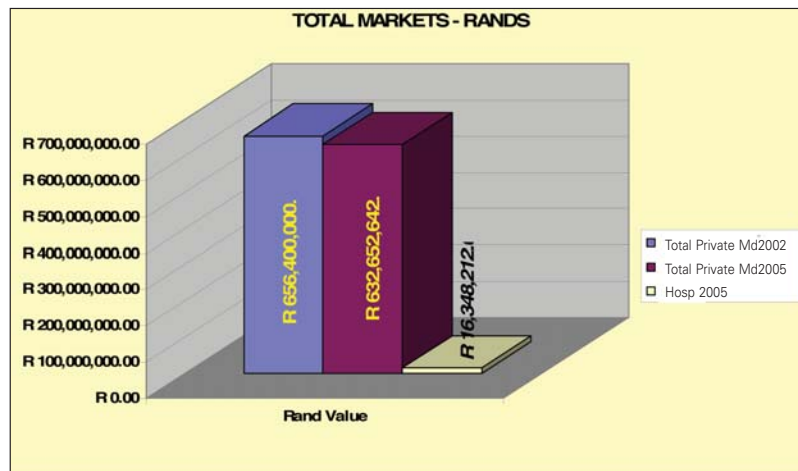


Fig. 4. 'Sinus' medications (ZAR value).

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although there are some significant exceptions for the more expensive drugs – small unit numbers diminish the importance. Together with the systemic antihistamines, seen below, these most likely represent the bulk of the OTC medicines – that is self-medication by the allergy-uneducated. Unfortunately, practice experience is that both OTC scripting to 'allergy-uneducated patients' and physician scripting is high for these drugs.

Patients appear to be relatively happy to pay these prices for what amounts to approximately one week of therapy. This indicates that resistance to steroid prices is due to lack of education and possibly funder misinformation especially as the antihistamine is now always an out-of-pocket expense.

As can be seen, the Total Private Market (TPM) uses more first-generation antihistamines and secondary drugs, (R05A0) than almost all the other drugs combined. As will be seen later, the apparent trend, from 2002 to 2005, of relative increase in the systemic antihistamines is not all good news, as many of these (units) are the so-called first-generation (older) drugs.

Another significant concern, no doubt brought about by the new legislation with pegging of pharmaceutical prices, as well as mandatory substitution, is that further analysis of these figures reveals that the ZAR costs (Fig. 4) hide these significant increases in unit sales (Fig. 5).

Funder reports of successful implementation in managed care almost always refer to ZAR values and therefore hide the increased unit sales. Fig. 6 gives the ZAR/unit data.

In addition, first-generation antihistamines have no effect on the most obtrusive symptom of allergic rhinitis, nasal obstruction, being most active in the acute allergic phase only.

A final concern is that the State hospital system appears to exhibit two major problems.

1. Poor exposure of hospital-based residents to respiratory drugs other than a small amount of antihistamines (first- and second-generation), the sum of which is further diluted by dermatological and acute non-respiratory allergy use in casualties. It is no wonder there are these poor prescription patterns. (Figs 2 & 3).
2. The hospital ZAR/unit cost – an extraordinary idiosyncrasy curiously left untouched by the recent legislative changes when one considers all the other playing fields were levelled by the introduction of the National Health Reference Price List (NHRPL) (Fig. 4).

Further evaluation of the figures reveals a number of disturbing trends that are emerging (Figs 7 & 8):

- The enormous increase in first-generation antihistamines (by units) that are prescribed (Fig 7).
- The impact that generic substitution/prescription appears to have on this market.

Obviously first-generation drugs are not legal generics of second-generation drugs, and substitution in this

case amounts to illegal therapeutic substitution. One ethical product has managed to 'buck this trend' – a superior drug or the product of superior marketing?

### Nasal corticosteroids

When one considers nasal corticoids, the gold standard of prescription drugs in allergic rhinitis, trends appear more acceptable (Figs 9 -11).

A remarkable decrease in ZAR value in nasal corticoid prescription is noted. There has been an approximately 13% increase in unit sales. This translates to roughly a 20% reduction in the average unit price of these drugs; therefore a real saving has been made.

Trends with the individual drugs in this category (Figs 12 & 13) reveal that mostly this change appears to be due to generic prescription and mandatory substitution. Therapeutic substitution, illegal but commonly seen in practice, remains a problem which is difficult to quantify.

### SIGNIFICANCE OF THESE FINDINGS

Antihistamines comprise a broad class of pharmacological agents that include the first-generation, centrally acting, H<sub>1</sub>-receptor antagonists (e.g. diphenhydramine) and the newer, second-generation, non-sedating H<sub>1</sub> blockers (e.g. loratadine). Other antihistaminic agents, such as cimetidine, work primarily on H<sub>2</sub> receptors causing inhibition of gastric secretion; still other experimental antihistamines act on H<sub>3</sub> receptors. While first-generation H<sub>1</sub>-receptor antagonists are responsible for the vast majority of poisonings, all antihistamine classes have been associated with serious toxicity.<sup>5</sup>

All H<sub>1</sub> antagonists are reversible competitive inhibitors of histamine receptors. First-generation H<sub>1</sub>-receptor blockers are also potent competitive inhibitors of muscarinic receptors and may cause the anticholinergic syndrome (e.g. agitated delirium sinus, dilated pupils, dry mucous membranes, dry skin, ileus, tachycardia and urinary retention). In addition, disruption of cortical neurotransmission and fast sodium channel blockage may occur. These effects exacerbate sedation and seizure activity and may cause widened QRS interval cardiac conduction delays. The phenothiazines class of antihistamines (e.g. promethazine) has alpha-adrenergic blocking activity and may cause hypotension.

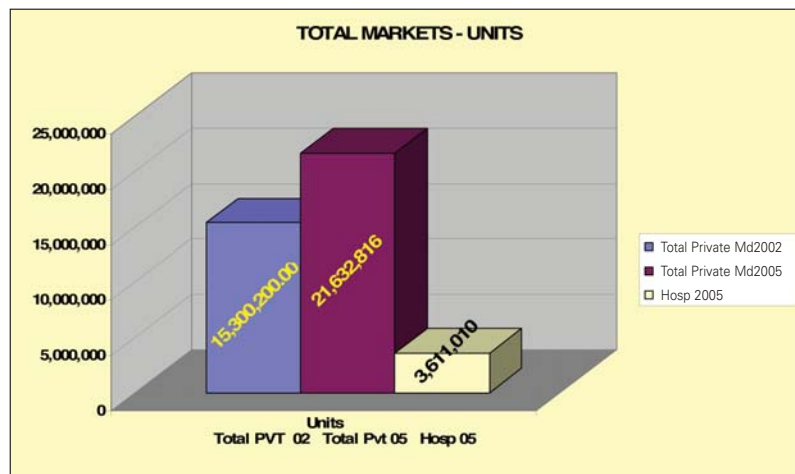


Fig. 5. 'Sinus' medications (units).

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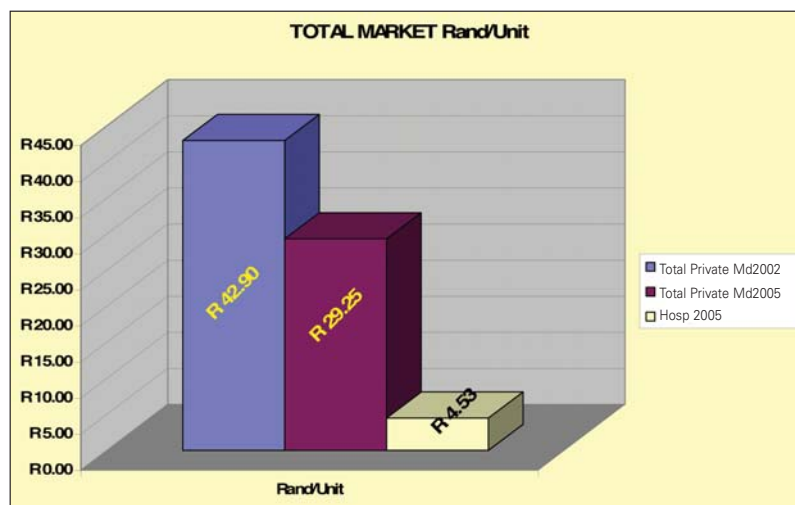


Fig. 6 'Sinus' medications (ZAR/units).

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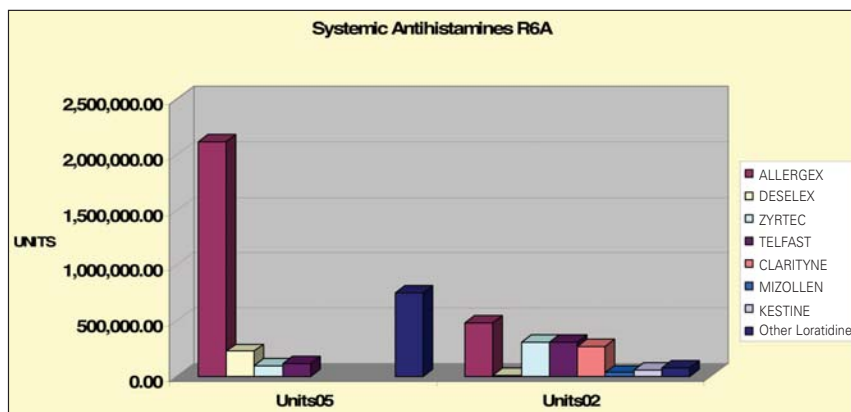


Fig. 7. R0A60 Systemic antihistamines (units).

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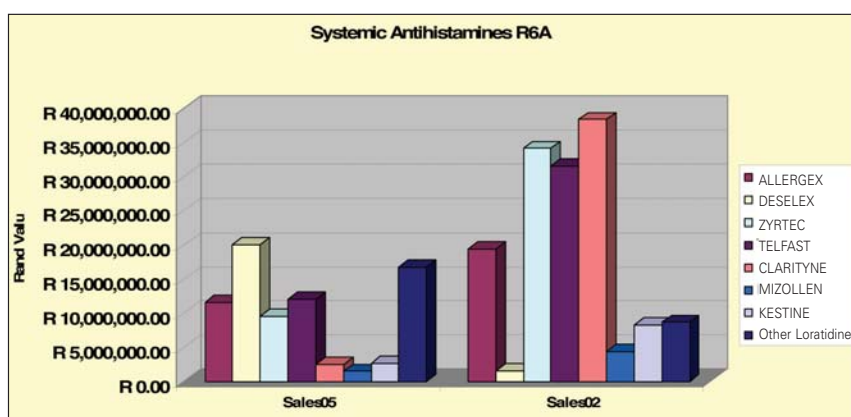


Fig. 8. R0A60 Systemic antihistamines (ZAR).

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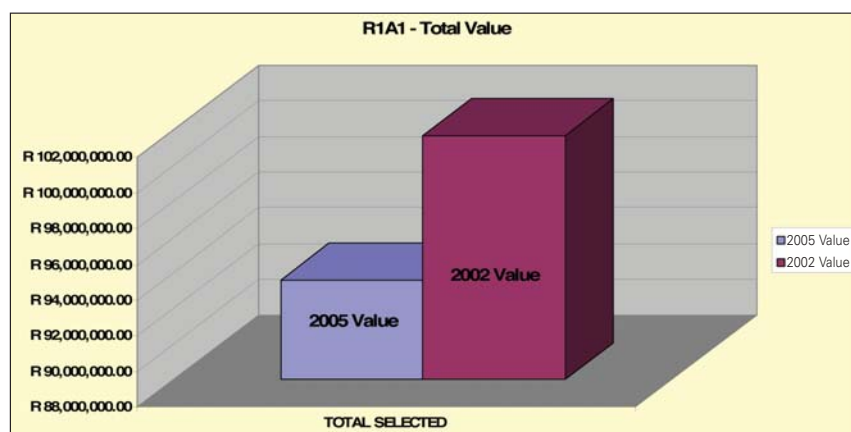


Fig. 9. R01A1 Nasal corticosteroids (total value).

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The six structural classes of antihistamines are as follows:<sup>5</sup>

1. Alkylamines (e.g. brompheniramine, triprolidine)
2. Ethanolamines (e.g. clemastine, diphenhydramine, doxylamine)
3. Ethylene diamines (e.g. tripeleonnamine)
4. Phenothiazines (e.g. promethazine)

diphenhydramine to a non-toxic metabolite twice as rapidly as white individuals and are much less sensitive to the effects on psychomotor performance and sedative effects.<sup>5</sup> Antihistamines are also capable of auto-induction of metabolism.

The greatest number of toxic antihistamine exposures is associated with patients younger than 6 years (22 854 or 46%).<sup>5</sup>

5. Piperidines (e.g. astemizole (off the market), fexofenadine, loratadine, terfenadine (off the market))

6. Piperazines (e.g. cetirizine, meclizine)

The American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC-TESS), 1999, ascribes 52 118 exposures to either H<sub>1</sub> or H<sub>2</sub> blockers.<sup>5</sup> H<sub>2</sub> blockers account for 5 721 exposures while H<sub>1</sub> blockers described above account for 46 397. A total of 17 632 patients were treated in a health care facility. Diphenhydramine was the most common antihistamine exposure.<sup>5</sup> Of these, 3 884 (7.4%) resulted in moderate-to-major toxicity and 28 (0.05%) resulted in fatality. Seventy-one per cent of fatalities were associated with diphenhydramine.<sup>5</sup>

First-generation H<sub>1</sub>-receptor antagonists, such as diphenhydramine, can be dangerous because they may cause pronounced agitation leading to rhabdomyolysis and acidosis and a quinidinelike sodium channel blocking effect may cause delayed conduction and contribute to ventricular dysrhythmias.<sup>5</sup>

Second-generation H<sub>1</sub>-receptor antagonists, such as terfenadine and astemizole (removed from market), may result in QT interval prolongation and life-threatening polymorphic ventricular tachycardia (torsade de pointes).<sup>5</sup>

Individuals of Asian descent can acetylate

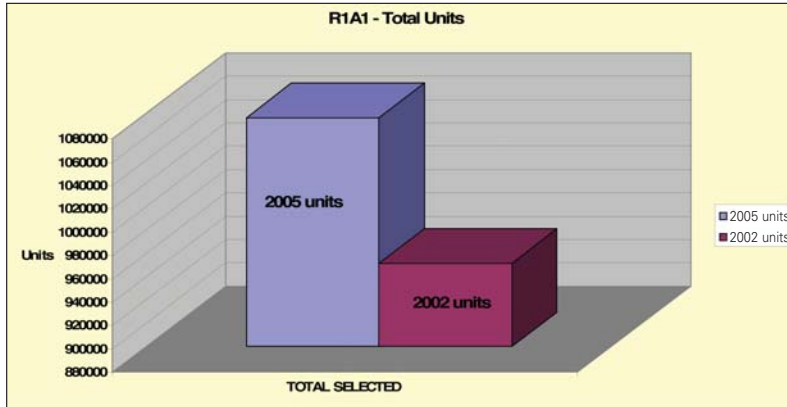


Fig. 10. R01A1 Nasal corticosteroids (total units).

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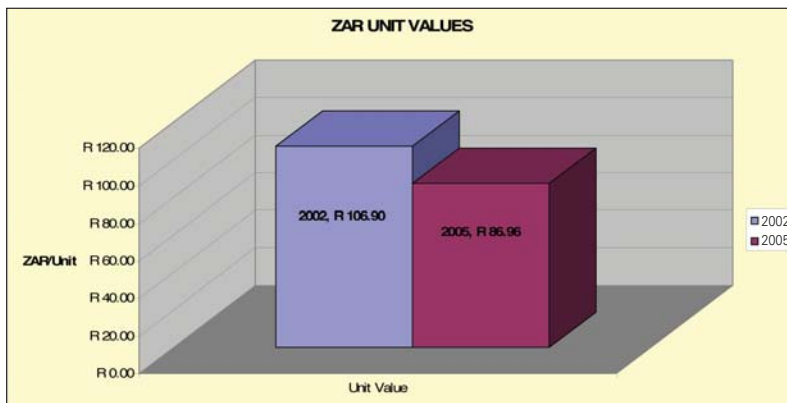


Fig. 11. R01A1 Nasal corticosteroids (unit value (ZAR)).

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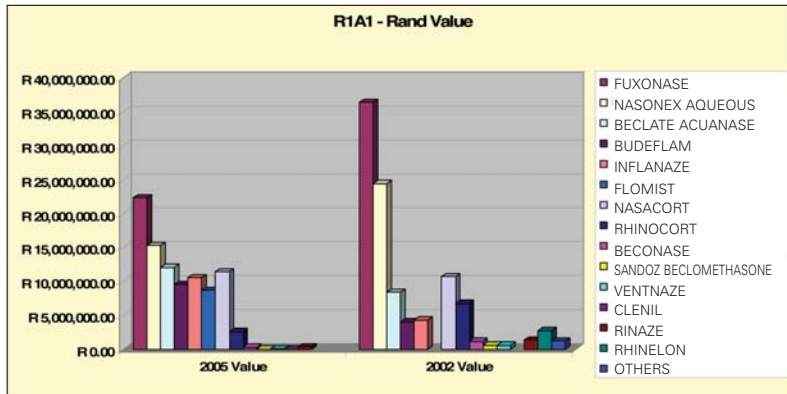


Fig. 12. R01A1 Nasal corticosteroids (rand values – individual drugs).

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The safety record of the second-generation drugs has not been without incident, but the withdrawal of responsible drugs has been fairly rapid and effective. The relative safety of the remaining drugs has been well documented.<sup>6, 10</sup>

In addition, in the USA, the use of first-generation antihistamines results in an additional 266 000 injuries and 1 100 fatalities (including motor vehicle, occupational, home and public injuries) per year in the USA. The total cost to USA society is \$7.4 billion.<sup>7</sup> According to Dr

John Weiler, 'Diphenhydramine has more impact on driving performance than alcohol does.'<sup>7</sup>

In many USA states, driving under the influence of 'sedating medications' is outlawed.

Safety of these drugs for this exceptionally common condition across all ages is a major problem that has all but been ignored by managed care.

There are also well established effects in children.<sup>2,9,10</sup>

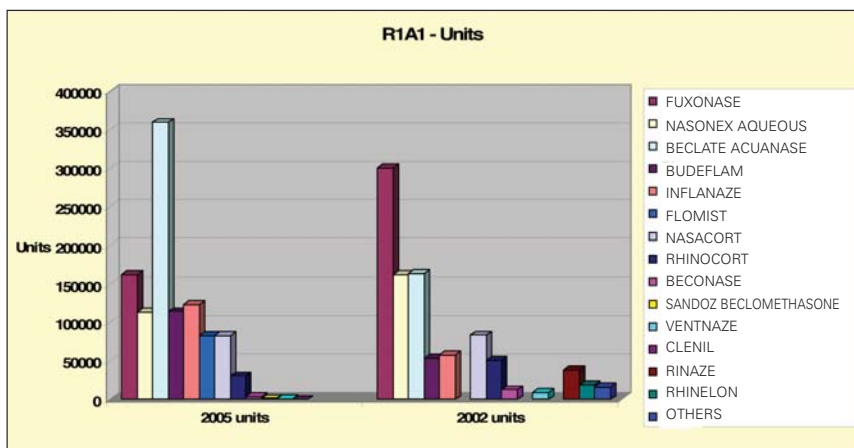
- Allergic children on antihistamines perform worst at school.
- Allergic children on no treatment or second-generation antihistamines and/or steroids perform better at school.
- Non-allergic children appear to do best of all.

When one looks comprehensively at the cost of treatment, it is clear that the less expensive alternative based on the cost per month of medication may not indicate the real cost associated with treatment. Actuarial studies have been done where modern actuarial and clinical concepts have been combined to test the hypothesis that the safety and productivity gains of using non-sedating treatments for allergies might more than offset the extra expense of these medications plus the costs of associated physician visits.<sup>4</sup>

They identified high co-payments to funders as a major driver towards the use of OTC drugs. They also recommended prohibiting the use of sedating medications in the workplace and promoted recognition of the broad prevalence of allergies in the workforce. Educating employees about workplace and non-workplace hazards of sedation and self-medication with sedating antihistamines, as well as education of employees and spouses of employees about allergen avoidance, is essential.<sup>4</sup>

Therefore when the managed care organisations and funders, as well as many pharmaceutical companies and a host of our colleagues and pharmacists, look at cost per disease on the basis of cost per month per member of treatment (ICD10 codes), the real costs of treatment are totally ignored.

In conclusion when one relooks at ARIA guidelines, probably the most important facets that need attention are:



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#### Declaration of conflict of interest

The author has received grants for educational activities from Sanofi-Aventis, GlaxoSmithKline and Schering Plough, all of South Africa.

Fig. 13. R01A1 Nasal corticosteroids (unit values – individual drugs).

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- Education relevant to the diagnosis of allergic rhinitis
  - The 'Dr I have sinus' problem probably still accounts for a significant part of the OTC chaos.
  - The practitioner armed with correct diagnostic expertise is the only practitioner with the prescription expertise – this does not only apply to general practitioners
  - The managed care organisations and funders must be brought into line or the risk and cost of their self-motivated cultures exposed.
- Concentration on the place for antihistamines and the appropriateness of antihistamine prescription OTC or otherwise.
- A very significant related problem, inappropriate antibiotic scripting in allergic rhinitis, can then be similarly addressed.

#### ACKNOWLEDGEMENTS

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#### Addendum

R05A0	Non anti-infective cold preps	CORENZA C, SINUTAB, BENYLIN FOUR FLU, SINUMAX, ADVIL CS, DEMAZIN SYRUP, SINUCLEAR, ADCO-SINAL CO, FLUSIN, CORYX, RINEX, FLUST
R06A0	Antihistamines systemic	1ST AND 2ND GENERATION
R01A1	Nasal corticoids without anti-inflammatory	FLUTICASONE, MOMETASONE, BUDESONIDE ETC.
R01A7	Nasal decongestants	ILIADIN, DRIXINE, VICKS ETC
R01B0	Systemic nasal preparations	DEMEZINE COLD, CLARITYNE D ETC
R01A4	Nasal anti-inflammatory without corticoid	VIBROCIL, LOCOBIOTAL, BACTROBAN
R01A9	Other topicals	DRIXINE SALINE, SALEX, STERIMAR
R01A6	Nasal anti-allergics	VIBROCIL S, DRISTAN, LIVOSTIN, RHINOLAST, CROMOHEXAL ETC.
R01A3	Nasal corticoid + anti-inflammatory	NASOMYXIN

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