

Adult growth hormone deficiency

Brief review and discussion of some
controversies in management

I M Holdaway
Endocrinologist
Auckland Hospital
New Zealand

The syndrome of adult growth hormone deficiency

GH-deficient individuals have variable clinical features ranging from minimal or no symptoms to major impairment

Symptoms include impaired psychosocial wellbeing, abdominal obesity, fatigue, reduced strength and exercise capacity, and reduced quality of life

Adverse changes in:

Body fat
Lean mass
Physical performance
Cardiovascular function
Insulin sensitivity
Lipid levels
Quality of life
Bone density
Mortality (?)

Effect of GH replacement

Improves
Improves
Improves
Improves
<->
Reduce
Improves
Increases
?

Growth hormone replacement treatment

Childhood:

Crude GH extracts trialed in 1930s (ineffective)

Treatment with purified cadaveric GH 1958 (Raben,)

Recombinant GH 1982 (Rosenfeld)

Adults:

First report of clinical improvement in an adult treated with GH was by Raben (1962)

Initial clinical trials of adult GH treatment:

- Jorgensen et al, Lancet 1989
- Salomon et al, NEJMed 1989

Local experience:

- Cuneo et al 1998
- Holdaway et al, 2015



Many studies of GH treatment in adults are observational

KIMS (Pfizer International database)

An observational database, some control data but not necessarily matched.

n = >2000

Noted: ↓ sick leave

↓ doctor visits

Better leisure time activity/satisfaction

Less assistance with daily living

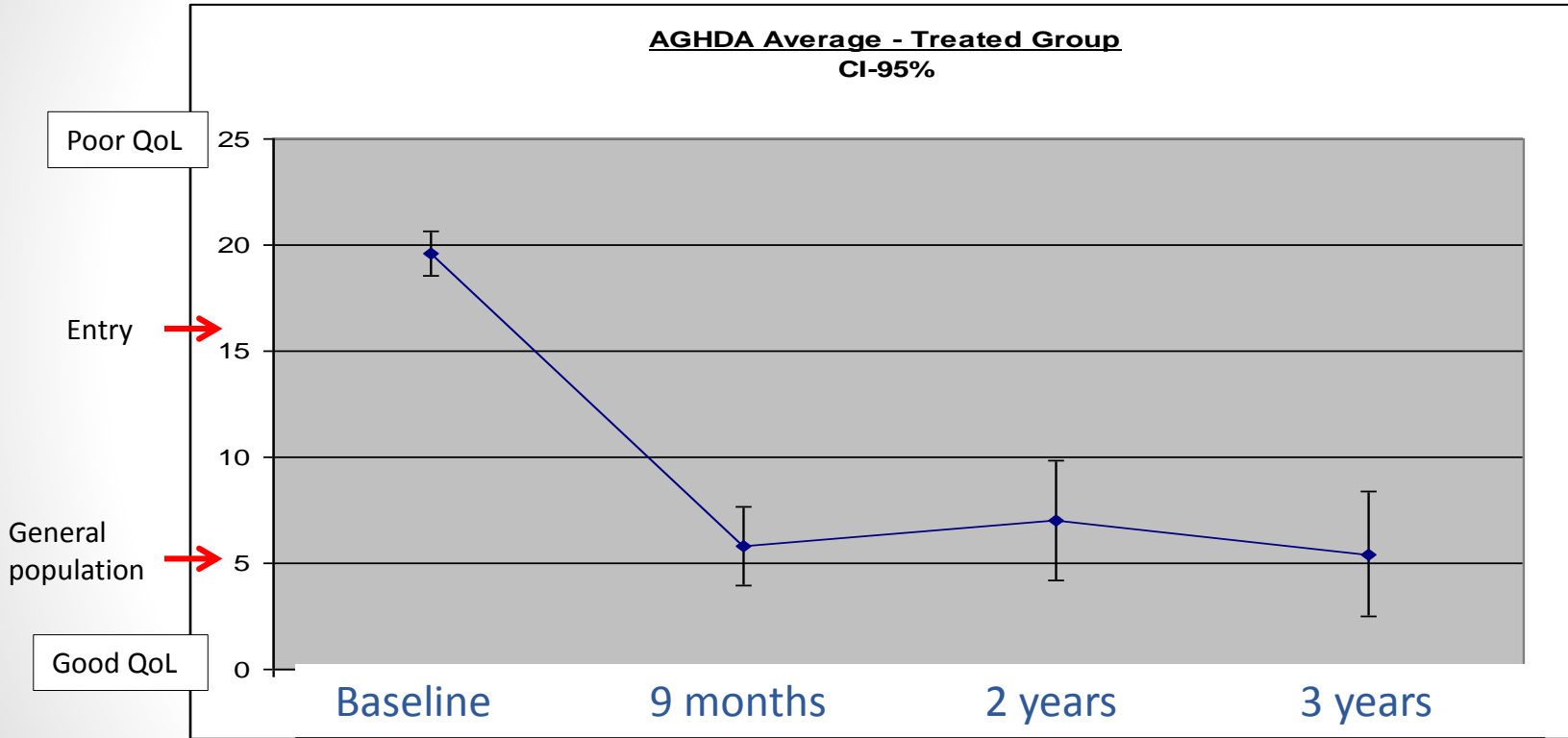
Improved Q of L scores

Sweden: Health care costs for hypopituitary patients = 2 x normal population, ↓ with GH treatment

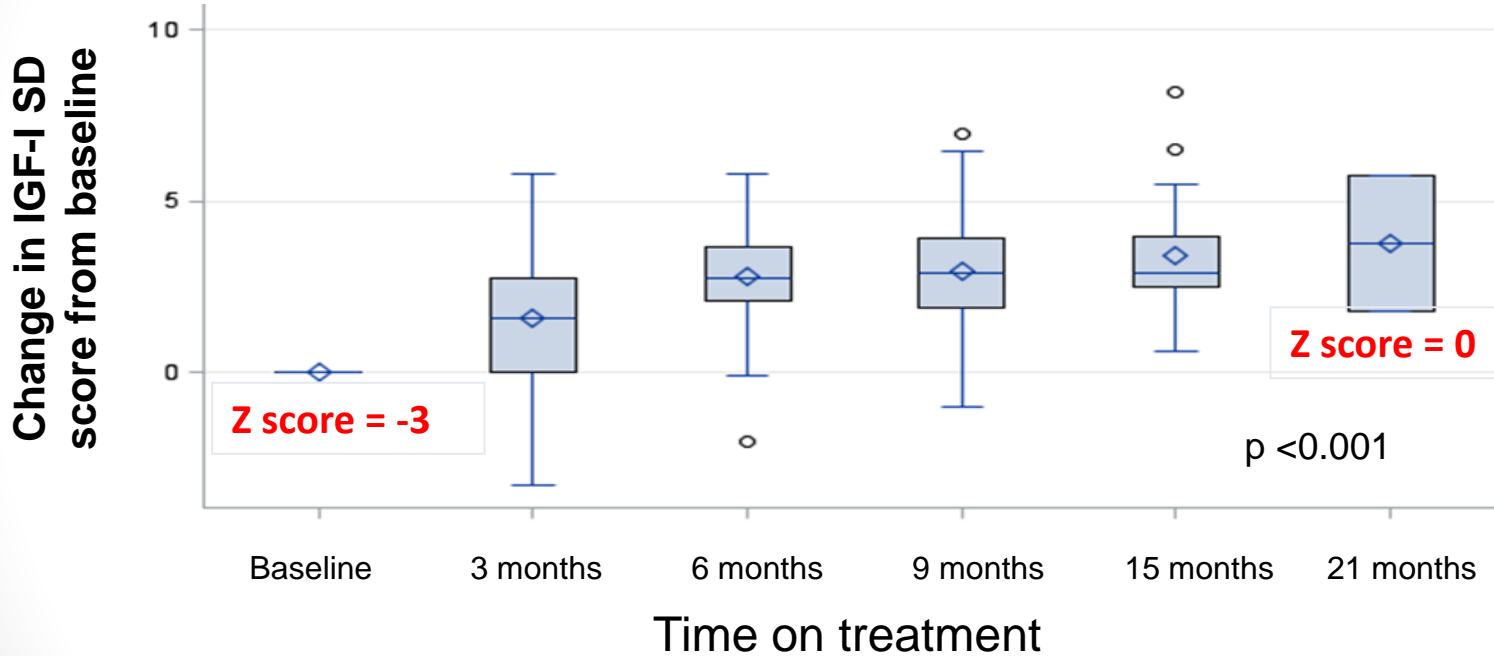
HypoCCS study (supported by Eli Lilly)

- 10 yr observational study in 1532 GH-deficient patients
- Assessed quality of life with the (QoL-H) questionnaire
- Significant improvement in QoL dimensions from mean z-scores of -1.5 to z-scores of -0.1
- There was greater improvement in those with:
 - no depression at entry
 - poorer QoL score at entry
 - lower BMI at entry

Change in QoL-AGHDA with GH treatment (NZ)



Change in serum IGF-I SD score with GH treatment (NZ)



Controversial/uncertain areas in the treatment of growth hormone-deficient adults with growth hormone

- How definitive is the database of randomised controlled trials of GH treatment for deficient adults?
- What are the safety issues of GH treatment?
- How durable are the treatment benefits?

**Analysis of randomised
controlled trials of GH
treatment of deficient adults**

NICE (UK) review of adult GHD

- 2 independent assessments of trial data:
 - Wessex Institute of Health Research, Southampton
(published RCTs and cost analysis)
 - University of Sheffield School of Health
(included unpublished and observational studies)
- Data:
 - 17 RCTs, ~ 900 patients, average 6/12 treatment
 - 23 different QoL tools
- Criticism of reviewed controlled studies:
 - Small numbers, short duration, different QoL scales,
randomisation not well described

NICE review

Quality of Life assessment

- **NHP questionnaire:** Some QoL profiles improved (especially social isolation, emotional reaction)
- **PGWS score** improved (psychological general wellbeing)
- Improvements much more marked in severely affected subgroups
- **QoL-AGHDA questionnaire:** on average improved 4 points, but if baseline score was ≥ 15 (poor QoL) then the average improvement was 12 points. On withdrawal of treatment patients could readily identify whether had been on GH or placebo
- Funded treatment proceeded based on the NICE recommendations

Canadian Agency for Drugs and Technologies in Health

Rapid Response Report March 2015

- Remit: To review evidence of clinical effectiveness, safety and cost-effectiveness for the use of GH replacement in patients age >25yrs with severe GH deficiency due to pituitary destruction
- Examined 1 Systematic Review, 13 non-randomised studies and the 2009 AACE guidelines for GH replacement

CADTH findings

- The review was critical of the analysed studies (small numbers, mixed aetiology of GHD, safety issues poorly described)
- No firm evidence for improved “direct” patient health outcomes
- No consistent impact on cardiovascular health outcomes (varied between studies)
- Quality of Life analysis was included in 9 studies (n = 520), showing consistent improvement in QoL with GH treatment. However, 2 studies showed some improvement in an untreated control group

Mayo clinic meta-analysis of the effects of GH treatment on body composition and quality of life

54 RCTs, data quality ranked as “fair”

Mean difference in body weight = -2.31kg (1.96-2.66)

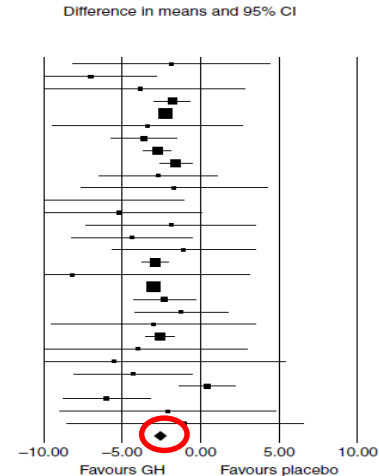
Mean difference in fat mass = -2.56kg (2.16-2.97)

Mean difference in lean mass = +1.38kg (1.1-1.65)

Quality of life scores improved in 11 of the 16 trials which reported QoL data

Change
in fat
mass

Statistics for each study				Sample size		
Difference in means	Lower limit	Upper limit	P value	GH	P	Total
-1.90	-8.18	4.38	0.55	23	13	36
-7.00	-11.21	-2.79	0.00	20	23	43
-3.87	-10.58	2.84	0.26	11	12	23
-1.82	-2.95	-0.69	0.00	30	31	61
-2.25	-2.95	2.16	0.00	59	57	116
-3.40	-9.47	2.67	0.27	7	6	13
-3.60	-5.69	-1.51	0.00	10	9	19
-2.77	-3.64	-1.90	0.00	60	55	115
-1.60	-2.62	-0.58	0.00	15	15	31
-2.70	-6.44	1.04	0.16	8	8	16
-1.70	-7.64	4.24	0.57	7	8	15
-12.30	-23.54	-1.06	0.03	10	10	20
-5.21	-10.46	0.04	0.05	14	15	29
-1.90	-7.31	3.51	0.49	26	33	59
-4.40	-8.22	-0.58	0.02	34	30	64
-1.10	-5.65	3.45	0.64	9	7	16
-2.90	-3.74	-2.06	0.00	34	34	68
-8.20	-19.48	3.08	0.15	5	5	10
-3.00	-3.14	-2.86	0.00	85	80	165
-2.30	-4.29	-0.31	0.02	14	15	29
-1.25	-4.21	1.71	0.41	13	14	27
-3.00	-9.50	3.50	0.37	9	9	18
-2.60	-3.51	1.69	0.00	19	16	35
-4.00	-10.95	2.95	0.26	13	11	24
-5.50	-16.41	5.41	0.32	11	12	23
-4.30	-8.10	-0.50	0.03	11	14	25
0.40	-1.41	2.21	0.66	16	14	30
-6.00	-8.78	-3.22	0.00	14	11	25
-2.08	-8.97	4.81	0.55	17	13	30
-1.00	-8.52	6.52	0.79	11	11	22
-2.56	-2.97	-2.16	0.00			



Side effects and safety of GH treatment

Side effects of GH treatment

Generally mild, rarely lead to discontinuation, dose dependent

German cohort treated in the KIMS database:

10 yrs n = 440	- Depression	1.6%
	- Headache	0.9%
	- Arthralgia	0.2%
	- Oedema	0.25%
	- new diabetes	1.4%
	- Recurrent neoplasia	2.5%

Australian study (Cuneo et al) = higher GH dose, higher rate of side effects

Safety in special situations:

Use of GH in those with meningiomas, OSA, active malignancy, previous acromegaly, pregnancy, Prader Willi

Follow-up of those treated in childhood (SAGhE report)

Safety and Appropriateness of Growth Hormone Treatments in Europe (SAGhE) studies

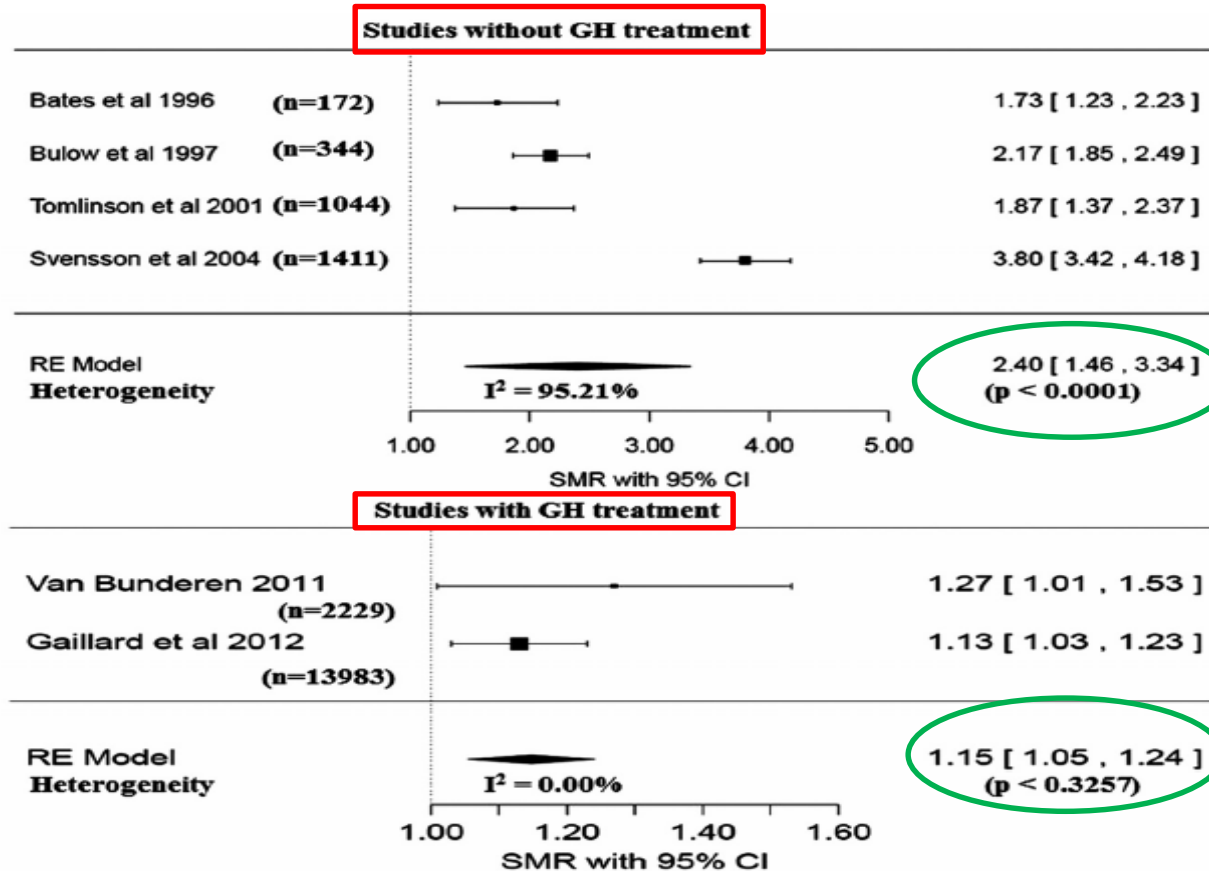
- SAGhE is a collaborative European study from multiple countries to assess long-term mortality in patients treated with GH in childhood for isolated GH deficiency, idiopathic short stature, and those born small for gestational age.
- An early report the French cohort (Carel 2012) suggested an increased long-term mortality, particularly from bone tumours and cardiovascular disease, in those treated with GH in childhood for the above indications (75% had isolated GH deficiency)
- A subsequent report including patients from Belgium, Sweden and the Netherlands (JCEM 97;E213, 2012) did not find any unexpected mortality increase
- The collaborative study is on-going in order to accumulate sufficient data to calculate SMRs

Long-Term Mortality after Recombinant Growth Hormone Treatment for Isolated Growth Hormone Deficiency or Childhood Short Stature: Preliminary Report of the French SAGhE Study

- Overall SMR, and univariate analysis of individual contributors to mortality, in 6928 “low-risk” patients treated with GH in childhood for ~ 4yrs
- Mean follow-up time 17.3 ± 4.1 years
- Average age at census/death 28yrs

Factor	Observed deaths	Expected deaths	SMR	95%
Overall	93	70	1.33	1.08-1.64
GH dose >50µg/kg/d	6	1.76	3.41	1.25-7.42
Cerebral haemorrhage	4	0.6	6.66	1.79-17.1
Bone tumours	3	0.6	5	1.01-14.6

Meta-analysis of studies of mortality in patients with hypopituitarism



Mortality in patients treated with GH in childhood and then as adults in the HypoCCS database

1024 patients treated with GH in childhood

3.7yr follow-up during adult GH treatment starting age 27yrs

Average GH dose 0.57mg/d

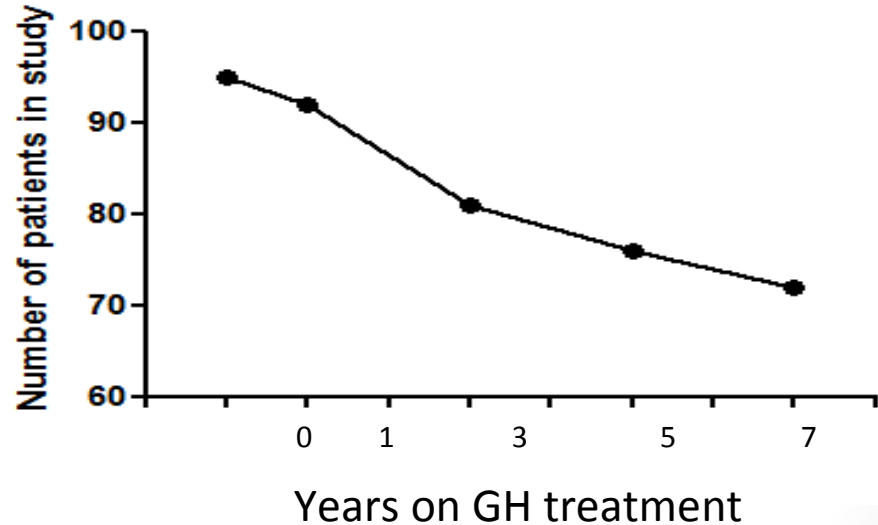
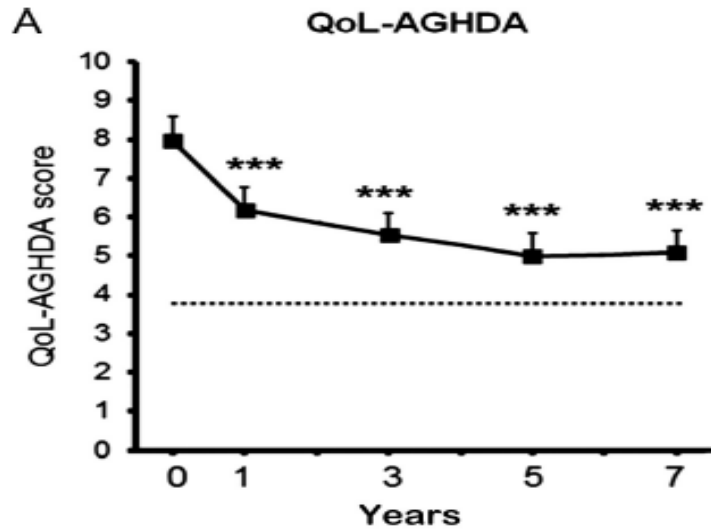
Table 2. Crude Mortality Rate and SMRs by Country for COGHD Group

Country	N	Follow-up years	Crude mortality (100,000 person-years) (95% CI)	Observed deaths	Expected deaths	SMR (95% CI)
Czech Republic	27	141.4	707.2 (17.9–3940.4)	1	0.299	3.35 (0.08–18.64)
France	125	372.2	806.0 (166.2–2355.6)	3	0.927	3.24 (0.67–9.46)
Germany	113	505.22	197.9 (5.0–1102.8)	1	1.12	0.89 (0.02–4.97)
Netherlands	66	474.74	210.6 (5.3–1173.6)	1	0.779	1.28 (0.03–7.15)
United Kingdom	40	160.81	1865.5 (384.7–5451.9)	3	0.278	10.81 (2.23–31.58)
United States	359	1134.8	88.1 (2.2–491.0)	1	1.931	0.52 (0.01–2.89)
Overall	1204	4462.4	224.0 (107.5–412.1)	10	8.751	1.14 (0.55–2.10)

Durability of response to growth hormone

Durability of AGHDA QoL change with GH therapy over 7 years

Open study, n= 95 patients, treated with 0.4mg GH daily



Possible reasons and contributors to cessation of GH treatment in the NZ program

- Adverse effects appear a rare cause for stopping treatment
- Individuals with less severe GH deficiency prior to treatment (higher IGF-I, AGHDA score only just reaching inclusion figure) were more likely to discontinue treatment
- Those discontinuing treatment often have more psychological symptoms at the start (? falsely elevating the AGHDA score)
- One individual had a large meningioma detected and GH therapy has been stopped
- It seems likely that treatment stops because patients have a perceived lack of benefit long-term

Adherence to long term therapies

WHO report 2003

In developed countries, adherence to long-term therapies in the general population is around 50% and is much lower in developing countries.

Antihypertensives:

USA 51% adherence
China 43% adherence

Asthma:

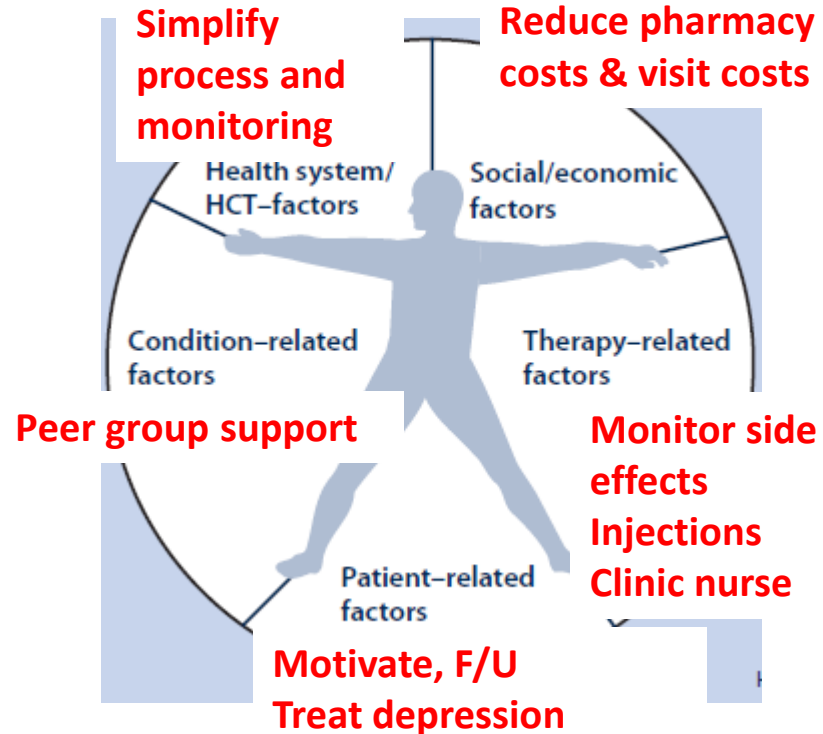
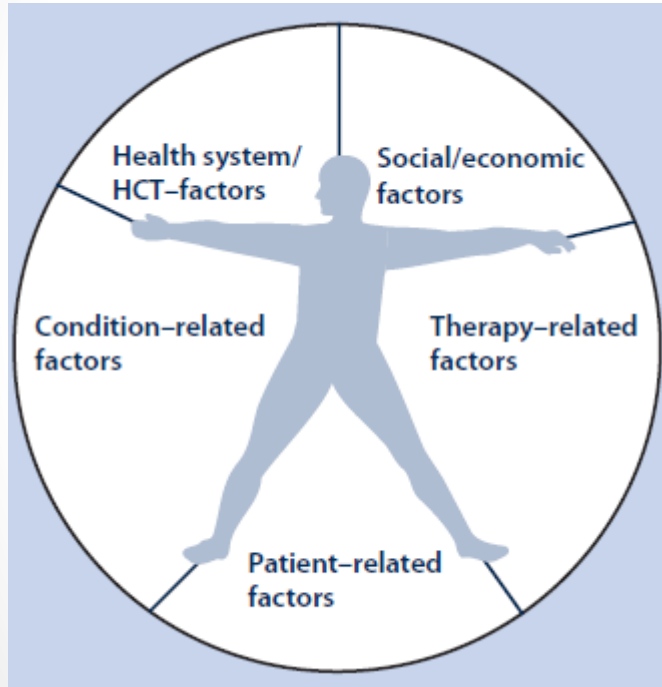
Australia 43% take asthma medication all the time as prescribed
28% take asthma preventers as prescribed

Depression:

Only 70% pick up prescriptions for a new agent, only 20% pick up tricyclic scripts after 6 months

The five dimensions of adherence

(WHO report 2003)



Summary

- A number of GH deficient adults have an important reduction in quality of life, which can be improved with GH replacement
- Although the base of randomised controlled trials to support this contention is limited, the data generally support treatment to improve QoL, with likely improvement in other dimensions
- To date, the safety of this treatment appears to be good, although long-term follow-up of those treated in childhood should continue
- Long-term adherence to treatment is around 50%, similar to treatment for other chronic conditions. Strategies to improve adherence are needed



NZ funded GH treatment program in adults (commenced 2010)

Application form for GH therapy (Pharmac)

Patient has a medical condition known to cause growth hormone deficiency.	<input type="checkbox"/> Yes <input type="checkbox"/> No
Patient has severe growth hormone deficiency defined as a peak serum GH level $\leq 3\mu\text{g/l}$ during an adequately performed insulin tolerance test, and/or $\leq 3\mu\text{g/l}$ in a 3-hr glucagon stimulation test, and/or $\leq 0.4\mu\text{g/l}$ in an arginine infusion test.	<input type="checkbox"/> Yes <input type="checkbox"/> No
Patient has a serum IGF-1 more than 1 SD below the mean for age and sex.	<input type="checkbox"/> Yes <input type="checkbox"/> No
Patient has a poor quality of life as defined by a score of ≥ 16 using the disease-specific quality of life questionnaire for adult growth hormone deficiency (QoL-AGHDA).	<input type="checkbox"/> Yes <input type="checkbox"/> No
Patient is being appropriately treated for other hormonal deficiencies.	<input type="checkbox"/> Yes <input type="checkbox"/> No